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RECURRENT COMPLETE HEART BLOCK WITH NORMAL CONDUCTION BETWEEN ATTACKS

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This report is made because there are relatively few such cases on record and because of the interest of certain respiratory observations made upon the patient in the presence both of the normal mechanism and of complete heart block.

Report of Case

The patient, a man, aged 70, complained of flatulence and epigastric discomfort. He had never had acute rheumatic fever and he denied syphilis. For twenty years he had suffered from indigestion and constipation. During the three years preceding his admission to the hospital he had had many attacks of syncope, which were preceded by dizziness and were brought on by straining at stool, by lying on his left side and by abdominal distension. During the attacks he became unconscious and often fell. Following the attacks marked nervousness and weakness frequently persisted for twenty-four hours. There had been no dyspnea or edema.

Examination showed no sign of heart failure; the heart was not enlarged; and no murmur was audible. The pulse was regular, 68 to the minute. The blood pressure was 130/85. There was a moderate grade of senile emphysema. The temperature was normal. The urine was negative. The Wassermann reaction was negative. The electrocardiogram showed a normal sinus rhythm with a normal conduction interval.

During the patient's stay in the hospital there occurred on several occasions abrupt attacks of syncope which lasted from one to two minutes. The pulse was never observed to be lacking, but when counted was always at a

rate of from 16 to 20 a minute. Following these attacks the pulse was about 30, as a rule for a few hours, once for two days. During these periods electrocardiographic records showed complete auriculo-ventricular dissociation. The patient showed no dyspnea, cyanosis or venous congestion. Electrocardiograms in the presence of the normal mechanism and of complete heart block are shown in Figs. 1 and 2. The record of Fig. 1 was secured in the interval between the attacks of complete dissociation. The effect of unilateral and bilateral vagal and ocular pressure during the normal sinus rhythm was very slight, the rate falling from 67 to 52 and the conduction increasing from 0.18 sec. to 0.20 sec. During a period of complete heart block the patient was given 2 mg. of atropin subcutaneously. In 35 minutes there was a reversion to the normal mechanism. Because there was no clear general effect of the drug it was not felt that this reversion could be definitely attributed to the atropin. The regular administration of small doses of atropin failed to prevent attacks.

The patient left the hospital unimproved and died suddenly six months later. In the interval the syncopal attacks had continued for a time, but the patient was entirely free of them for four months previous to his death.

The electrocardiographic records which are briefly analyzed in Table I need no special comment. No abnormal lengthening of the conduction time was ever observed. There are, however, constantly present the forms associated with a partial block of the left bundle branch, which is more marked in the presence of complete dissociation. The auricular arrhythmia (consisting of slowing of the rate during ventricular diastole), commented upon by Wilson and Robinson [1] and by Lewis,[2] was not present.

The data of Table II, although they are isolated observations, are of interest for certain physiological implications. The great drop in the ventricular rate with the complete dissociation was accompanied, as would be expected, by a fall in the diastolic blood pressure. There was slight decrease in the vital capacity, but no significant change in the respiratory rate or in the minute volume. As mentioned above, the patient showed no trace of cyanosis or venous congestion during the periods of complete heart block; nor was there any real limitation of his activities over that usually present. It cannot, therefore, be supposed that there was any significant anoxemia, especially since it has been shown that the skin and peripheral parts bear the brunt of an ischaemic anoxemia.[3] This means that the resting circulatory minute volume must have been approximately as great with the complete heart block as it was with the sinus rhythm, and that the ventricular output must have increased almost in proportion to the fall in the ventricular rate. Although it must be admitted that the evidence is not conclusive, the facts are much against the point of view supported by Henderson,[4] who believes that the ventricular output is practically always maximal.

Notwithstanding the absence of dyspnea, there was observed a fall in the carbon dioxide tension of the expired and alveolar air which corresponds to the change seen in cardiac dyspnea, of which we do not at present know the explanation. The carbon dioxide tension rose again with the return of the normal rhythm. These observations were preceded by the usual rest period.

The data of eight cases in the literature which include all the cases we have found which definitely fall in the group to which our patient belongs, together with the data of this report, are given in Table III. Two cases (Nos. 10 and 11) in which heart block persisted are added because of the suddenness of the onset of the dissociation. Most of the instances previously reported have also occurred in elderly persons whose previous history throws no light upon the etiology of the condition. In only one case (No. 5) does it seem likely that a rheumatic infection could have been the basis of the disease. In another case (No. 6) it is possible that the auriculo-ventricular dissociation followed an acute infection of unknown nature. The most significant finding seems to have been general vascular sclerosis. The reported cases of abrupt transient auriculo-ventricular dissociation are rather few in number, but the data available suggest that they are usually not fundamentally different from other cases of progressive heart block. Of the eleven patients included in Table III (nine only showing transient auriculo-ventricular dissociation) seven are known to have developed permanent complete heart block, and nine died within a relatively short time. In the only instances in which an examination of the heart was made (Nos. 4, 7 and 8) definite lesions of the auriculo-ventricular bundle were found. As a rule, during the period of dissociation atropin was ineffective in relieving the block. In the only instance (No. 8) in which vagal influence during the sinus rhythm was reported to be marked, at autopsy the bundle was found to be severely damaged. Several of the cases showed various lesser degrees of heart block immediately preceding and following the complete dissociation.

In the light of a modern physico-chemical hypothesis of the nature of the conduction process, it may be inferred that there exists a large reserve in the conducting capacity of the auriculo-ventricular bundle which may be seriously encroached upon before conduction is measurably impaired. A few intact fibres may, under favorable circumstances, serve to carry on the conduction process normally; while some subtle local circulatory deficiency or a temporary increase in vagal action may result in failure of the few remaining fibres to function. Thus, in Case No. 8 the re-establishment of vagal influence following exercise, the act of swallowing and pressure on the vagus brought on abruptly complete dissociation. This point of view is also helpful in understanding the reported instances of lesions affecting the auri-

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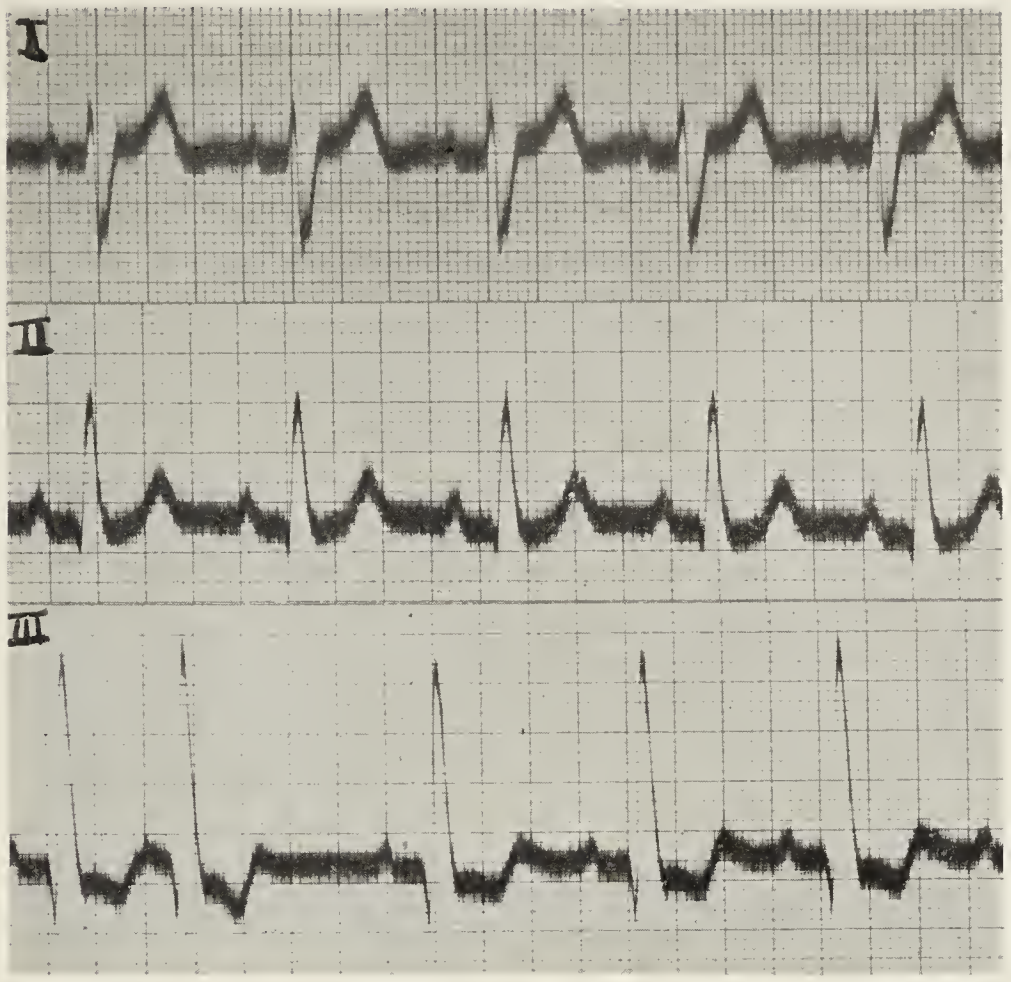

Fig. 1.—Electrocardiogram showing the normal mechanism taken April 14, 1922, between two attacks of complete dissociation. Leads I, II and III.

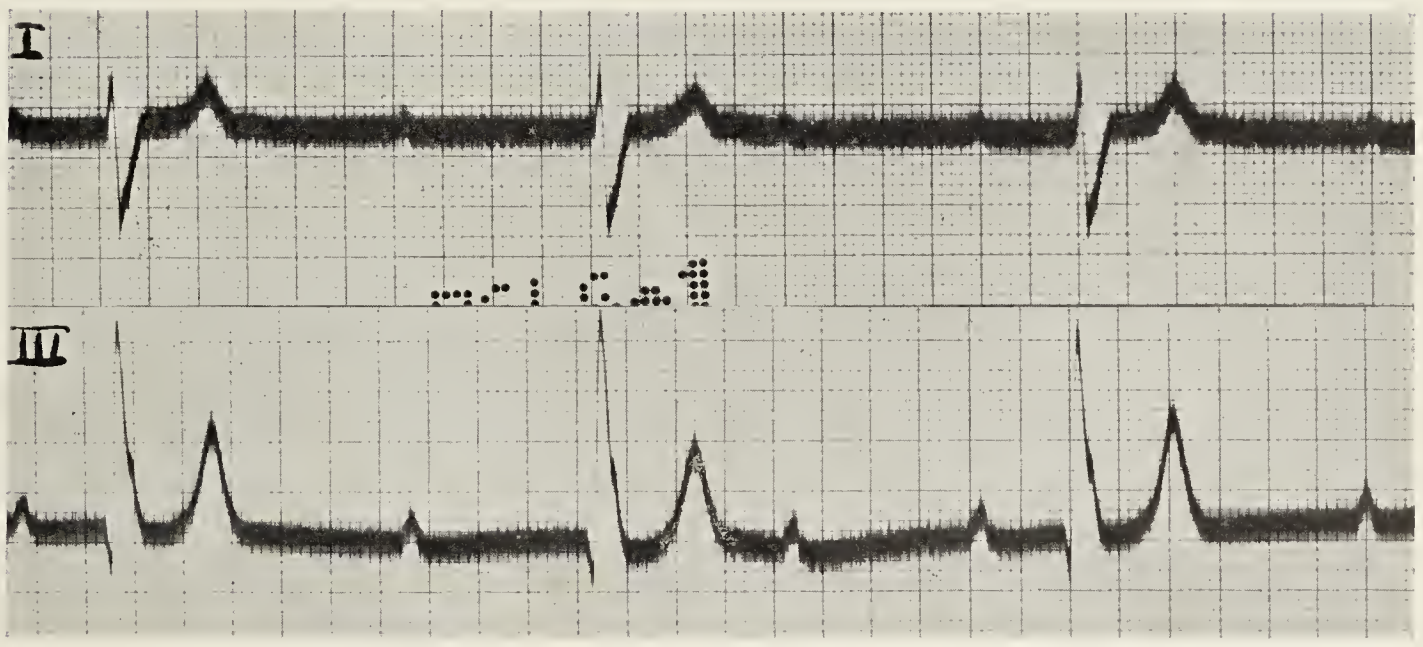

Fig. 2.—Electrocardiogram showing complete A-V dissociation taken April 11, 1922. Leads I and III. Note change in T wave in Lead III.

TABLE I.
Electrocardiographic data.

Date	Rate	P-R	QRS	Diagnosis
Apr. 11	Aur. 78 Ven. 30	....	0.15 sec.	Complete heart block. Partial left bundle branch block
Apr. 14	78	0.17 sec.	0.12 sec.	Normal mechanism. Partial left bundle branch block

TABLE II.
Clinical data.

Cardiac Mechanism	Date April 18 and 21	Date April 19
	Normal sinus rhythm	Complete heart block
Pulse Rate	68	20
Blood Pressure	130/85	128/60
Vital Capacity	70% normal	60% normal
Respiratory Rate	14	16
Resp. Min. Vol.	3,470 c.c.	3,350 c.c.
Tidal Air	250 c.c.	210 c.c.
Exp. CO_2	3.11%	2.82%
Alv. CO_2	6.06%	5.63%

culo-ventricular bundle in which no heart block had been recorded.

The warning of Lewis [13] may, therefore, be repeated that the atropin test is not necessarily decisive as to the pathogenesis of heart block; and that, when such an apparently marked vagal action as release from complete heart block is encountered, this response may take place because of the existence of an anatomical lesion which is already dangerously near causing permanent dissociation.

SUMMARY

1. A case of intermittent complete heart block and syncope with normal auriculo-ventricular conduction intervening is reported.

2. Respiratory and clinical data suggest that the resting ventricular output must have increased in the presence of heart block almost in proportion to the fall in rate.

3. The reported cases of this type indicate that there is usually a progressive anatomical lesion of the auriculo-

TABLE III.

Case No.	Author	Sex	Age	History	Records	Conduction time		Effect of atropin	Result	Necropsy findings
						Before attack	After attack			
1.	Gossage [5]	F.	71	Negative	Polygraphic and electrocardiographic	a-c 1/5″	a-c 1/5″		Unknown	
2.	Earnshaw [6] Thayer and Peabody [7]	M.	53	Negative	Polygraphic	a-c 1/5″	a-c 1/5″	No relief from gr. 1/30	Perm. Dissoc. Death	
3.	Mackintosh and Falconer [8]	M.	74	Negative	Polygraphic	a-c 1/5″	a-c 1/5″	No. attacks after gr. 1/100 t.i.d.	Death	
4.	Cohn, Holmes and Lewis [9]	F.	80	Acute rheumatic fever	Polygraphic	a-c 1/5″	a-c 1/5″ dropped beats		Death	Large venous sinuses in bundle. Sclerosis of node.
5.	Lewis [10]	M.	48	Aortic stenosis	Polygraphic	a-c 1/5″	a-c 1/5″ dropped beats	No effect	Perm. Dissoc. Death	
6.	Wilson and Robinson [1]	F.	48	Acute Infection ?	Electrocardiographic	?	dropped beats P-R 0.38″ P-R 0.20″	No effect	Partial Dissoc. Death	
7.	Russell-Wells and Wiltshire [11]	M.	44	Negative	Electrocardiographic	P-R 0.20″	P-R 0.20″		Perm. Dissoc. Death	Calcareous nodule below node and bundle. Sclerosis.
8.	Starling [12] Lewis [13]	M.	51	Negative	Polygraphic	a-c 1/5″	a-c 1/5″	Relief from gr. 1/33	Perm. Dissoc. Death	Calcareous nodule below node and bundle. Sclerosis.
9.	Present	M.	70	Negative	Electrocardiographic	P-R 0.17″	P-R 0.18″	No effect	Perm. Dissoc. Death	
10.	Mackintosh and Falconer [8]	M.	55	Negative	Polygraphic	a-c 1/5″	Dissoc. persisted		Perm. Dissoc.	
11.	Simon and Robinson [14]	M.	68	Acute rheumatic fever	Electrocardiographic	P-R 0.19″	Dissoc. persisted	No effect	Perm. Dissoc. Death	

ventricular bundle and that the prognosis is very unfavorable.

4. The warning is repeated that the atropin test is not necessarily conclusive as to the pathogenesis of heart block.

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UNIVERSAL LYMPHATIC LEUKEMIA OF THE SKIN

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The cutaneous manifestations of lymphatic leukemia are divided into two groups. In the first, non-characteristic eruptions such as urticaria, prurigo-like papules, purpuric areas and pigmentations occur. In the second group, pathologic changes similar to those found in the glands and internal organs in this disease are found. These changes are most frequently encountered in circumscribed nodules or patches, but occasionally the entire integument is diffusely implicated in this pathologic process, giving rise to a generalized dermatitis with more or less infiltration and exfoliation.

The object of this paper is to report a case of this type in which the blood showed the changes of lymphatic leukemia.

Report of Case.—The patient was a farmer, aged 63 years. Nothing important was noted in the family and past histories. He had had regular habits and had enjoyed good health up to the time of the present illness.

Present Illness.—Began in October, 1920, 10 months before examination, with excessive itching of the feet and calves of the legs. As a result of scratching, the skin was frequently excoriated to the extent that bleeding occurred. Two months later the itching was felt over the entire body, including the face, and soon afterwards he noticed definite thickening and reddening of the skin especially pronounced on the palms and soles. About 5 months after the onset the hair of the scalp and eyebrows began to drop out and scale formation became pronounced. At the beginning of his illness the itching was more troublesome during the night, but with the lapse of time it became his constant and most distressing symptom. It was intensified by exposure to cold rather than to heat. The thickening and discoloration of the finger-nails and toe-nails developed gradually. Although greatly handicapped, he managed to work on his farm until early in August, 1921. At last he was compelled to give up his work because of the gradual development of swelling of his feet, ankles and legs, and because the skin of the hands had become so thick that it would crack on the slightest exertion. There had been no weeping areas or nodular formations anywhere on the body. The patient did not know whether there had been any loss of weight. Physically, he felt fairly well and quite strong at the time of the examination.

Physical Examination.—He was well developed and well nourished. There was some ectropion with a mild bilateral blepharitis. The teeth were in very bad condition with marked recession of the gums and pyorrhea. The tonsils were not enlarged. The anterior and posterior cervical glands were just palpable. The axillary and inguinal glands were enlarged to the size of English walnuts. They were discrete, firm and freely movable. No glands could be felt in the abdomen. There was very definite retromanubrial dullness which extended 4 cm. to the right and 5.5 cm. to the left of the mid-sternal line (an x-ray of the chest confirmed this finding and strongly suggested enlarged mediastinal glands). The area of splenic dullness measured obliquely 11 cm. and 8 cm. in width. The edge could not be definitely felt. There was no tenderness in the splenic region. The liver dullness extended from the fourth rib to the sixth interspace in the mid-clavicular line and to the eighth interspace in the mid-axillary line. The edge could not be felt.

The entire cutaneous surface showed a profuse scaling and diffuse reddening (Figs. 1 and 2). The scales were thin, whitish or grayish, varying in size from a bran flake to a finger-nail and were so bountiful that the floor was covered with them when he undressed for examination.

After the use of a bland ointment for a few days, most of the scales had come off and the character of the changes was better observed. There was then apparent a generalized diffuse infiltration of the skin with mild accentuation of the normal lines. The color varied from a pinkish red on the face to a dark bluish red on the extremities. The epidermis in areas entirely free from scales had an unusually translucent appearance and small hemorrhages and pigmented spots were in some places clearly visible. The horny layer seemed to be thinner than normal, and when a partially detached scale was forcibly removed, bleeding was produced.

Although the infiltration was in general diffuse over the entire skin, some irregularity in the thickening on the thighs gave a slight mosaic appearance. The scalp was covered with a thick mass of whitish scales and there was a considerable loss of hair and beard, with almost complete absence of the eyebrows and eyelashes. The hair on the rest of the body also was very thin. On the anterior surfaces of the ankles the skin had thickened with papillomatous formation. In some areas the papillae were smooth and from 1 to 3 mm. in diameter; in other areas thickly massed small filiform verrucae had formed (Fig. 3).

There was extensive hyperkeratosis of the palms and soles (Fig. 4), with a formation of thick, blackish, partly detached plates which caused contraction of the fingers. There were some fissures on the fingers and also on the feet which were quite painful, so that walking was difficult. The nails (Fig. 5) were very much thickened at their free ends, which gave them a wedge shape. They had a black dirty color and offered about the same resistance to cutting as a piece of dried beef. The cut surface had a grayish color with pigmented streaks. They were loosely attached and could be pulled off with ease, leaving a pulpy nail-bed which bled easily.

There was no œdema anywhere on the body. Small subcutaneous hemorrhages could be produced by pinching the skin between the fingers.

Laboratory Examinations.—The patient was under observation from August 15, 1921, to October 10, 1921. The examination of the blood on August 18, 1921, was as follows:

I. Stains: Wilson's, Ehrlich's and Goodpasture's oxydase stain.

II. Red blood cells:
1. Number: 4,304,000.
2. Size. Marked anisocytosis; numerous microcytes, but few macrocytes.
3. Color. Moderate achromia. Haemoglobin 83% (Sahli).
4. Regeneration forms:
   a. Nucleated red blood cells: none seen in a count of 300 white blood cells.
   b. Basophiles: none present.
   c. Cabot's rings: none seen.
5. Resistance to hypotonic salt solution was within normal limits; hæmolysis began at .42 and was complete at .28.

III. White blood cells:
1. Apparent number (relative to red blood cells) 151,600.
2. Differential count: (300 cells)

Type of cell	Number counted	Absolute number	Per cent
P. M. N.	33	16,676.0	11
P. M. E.	3	1,516.0	1
P. M. B.	0	0.0	0
Small lymph.	214	108,090.8	71.3
Large lymph.	3	1,516.0	1
Small lymph. (Reeder type nucleus)	19	9,550.8	6.3
Pathological lymph.	6	3,032.0	2
Bilobed nucleated lymph.	12	6,064.0	4
Mononuclears	1	454.8	0.3
Transitionals	0	0.0	0
Myelocytes	6	3,032.0	2
Myeloblasts	3	1,516.0	1
	300	151,448.4	99.9

3. Presence of abnormal forms: There were many fragile white blood cells in the smear. These were ignored in the differential count. Special note is made that in counting 300 cells there were twelve lymphocytes seen which contained two distinct nuclei.

IV. Platelets. A number of smears were examined for the platelets, and although no count was made, they did not appear to be increased in number. In general, they were small and no pseudopodia were seen.

V. Parasites. None were seen.

VI. Special stains.
1. Oxydase reaction, (Goodpasture). A smear which was examined revealed 7% myeloid cells and 93% lymphoid cells.
2. Vital staining of the red blood cells with cresol blue (Pappenheim) showed two reticulated cells in a count of 1000 cells—a normal number.

VII. Summary of important evidence:
1. Red blood cells reduced in number with all the characteristics of a secondary anemia.
2. White blood cells showed a marked increase in number with a relative decrease in the polymorphonuclear leukocytes and an absolute increase in the small lymphocytes. Myeloid cells were present and numerous abnormal lymphocytes. The total of the lymphoid elements was 84.6%; of the myeloid elements 15.3%. The oxydase reaction revealed an even greater number of lymphoid elements.

VIII. Diagnosis of the blood picture; Chronic lymphatic leukemia.

The Wassermann Reaction was negative. The fasting blood sugar was normal—93 mg. per 100 c.c. of blood.

The basal metabolism (Sanborn-Benedict Apparatus) gave a metabolic rate of plus 51. (The normal rate varies between plus 10 and minus 10. The expected consumption of oxygen for a normal individual per minute per

square meter of body surface is 126 c.c. This patient consumed 191 c.c.). He showed no symptoms of hyperthyroidism.

There was an achylia gastrica with a free HCl deficit of 11%.

The urine revealed repeated traces of albumin and there were a few pus cells. No Bence-Jones protein was found.

The stool examination was negative.

Course and Treatment.—The patient was put into the hospital for observation and treatment where he remained from August 25, 1921, to October 10, 1921. Various ointments were used, but vaselin was found to be as valuable as any local application for relieving the stiffness of the skin and the excessive scale formation. He complained most of the time of a "freezy" feeling or a "crawly" sensation as if insects were on him. He was continually picking at the scales and rubbing himself with his palms. There were never any weeping areas on the skin except between the toes and occasionally from a small fissure or excoriation on the fingers. No nodules formed and there was no œdema. His temperature never rose above 99.6° and there was no loss of weight. For the first three or four weeks he was quite hopeful and cheerful, but gradually became depressed. X-ray treatments were given at first to the skin, and radiation to the glands and spleen was begun later, but the patient did not remain long enough to test the value of the latter. These treatments with the blood counts are tabulated in Chart I. Fowler's solution and Blaud's pills were given during the last four weeks of his stay. On the whole, treatment brought about very little improvement.

The horny plates on the palms and soles were gotten rid of by binding them in vaselin and giving x-ray treatment. At the end of the first course of x-ray treatments the scale formation seemed to have been appreciably reduced and the infiltration appeared to have decreased, leaving in some areas, especially about the shoulders and buttocks, a cigarette-paper-like wrinkling. There was, however, no definite fading of the color. During the treatments the right buttock was given by mistake H2 S. D. x-rays. In about two weeks this was followed by a diffuse oozing dermatitis which, however, healed up very quickly. A raw oozing area the size of the palm of the hand healed up to fingernail size in three days time with no treatment except the application of a boric acid dusting powder. This and also the excessive scale formation illustrates the rapid proliferative activity of the epidermal cells in this case. At first the burnt area appeared somewhat paler than the surrounding skin, but the scale formation was not diminished, and after about 10 days the color had returned to its former intensity and the area did not differ from the surrounding surfaces.

At the conclusion of the x-ray treatments to the skin there was a considerable drop in the number of white blood cells, but at the time the patient left the hospital the number was greater than when he entered. He returned home on October 10, 1921, and died in December of the same year, about 14 months after the onset of the skin manifestations. We were informed by one of his attendants that soon after he returned home his body began to enlarge, the legs became swollen and oozing fissures formed. About two weeks before he died, however, "the whole body just swagged right down and what skin was left just appeared to cleave to the bone." This very vivid description suggests that there must have been a rather rapid premortem disappearance of the infiltration in the skin.

Histologic Examination.—Tissue was excised from (1) the anterior surface of the thigh; (2) a papillomatous area on the ankle; (3) from the thigh, ten days after H1 S. D. x-rays; (4) the area of x-ray dermatitis on the buttocks.

These tissues were fixed partly in formalin and partly in Zenker's solution. Some were cut in celloidin and others in paraffin. The stains used were hematoxylin and eosin, Van Gieson's connective-tissue stain, polychrome methelyne blue and Giemsa's and Wilson's blood-cell stains.

1. *Anterior surface of thigh.*—(a) The horny layer was moderately thickened with parakeratosis and some loosely attached scales (Figs. 6, 7). The granular layer was absent in most parts of the sections. The rete layer showed in general considerable hypertrophy with intercellular œdema except over the papillæ where it was often atrophic. There was a rather uniform prolongation of the pegs. Some of them were thickened, some were club-shaped, while others were narrow and thin and tapered down to two or three cells in width. Secondary branching was common and very thin long sprouts were occasionally seen. The rete cells were in general swollen and had large well-stained nuclei, but in some areas there was atrophy and degeneration.

Throughout the whole epidermis there were numerous vesicle-like roundish spaces partly or completely filled with small lymphocytes showing dense black-staining nuclei. These were found in the pegs, throughout the rete and between the lamellæ of the horny layer. These small cells were also diffusely scattered between the epidermal cells where they showed various migratory shapes.

(b) *Cutis.*—Here a band of cellular infiltration with a marked uniform depth extending through the papillary layer and the upper part of the reticular layer was found (Fig. 8). It was sharply defined below, with occasional prolongations around the blood vessels, sweat glands and hair follicles. The infiltration in the lower portion of this band was very dense (Figs. 6, 7). Nothing remained of the normal architecture except an occasional hair follicle and here and there a strand of richly cellular connective tissue. In the papillary layer the infiltration in

CHART I.

X-ray treatments and blood examinations.

Date	X-ray treatments	Hem'gl.	W. B. C.	R. B. C.	C. I.	Lymphoid Elements	Myeloid Elements
8/18/21	.....	80%	140,000	4,000,000	1.0	82%	18%
8/19/21	.....	83%	151,000	4,304,000	0.9	92%	8%
8/25/21	.....	80%	160,000	4,320,000	0.9	——	——
8/29/21	Two applications HI S.D.*						
8/30/21	" "						
8/31/21	" "						
9/ 1/21	" "	70%	184,400	3,520,000	1.0	88%	12%
9/ 2/21	" "						
9/ 3/21	" "						
9/ 5/21	" "						
9/ 6/21	" "						
9/ 7/21	" "	70%	102,000	3,680,000	0.9	92%	8%
9/ 8/21	" "						
9/ 9/21	" "						
9/10/21	" "						
9/12/21	End of first	70%	148,000	3,760,000	0.9	92%	8%
9/14/21	course	70%	120,000	3,936,000	0.8	90%	10%
	Second course						
9/16/21	Two applications						
9/17/21	" "						
9/19/21	" "						
9/21/21	.....	60%	98,000	3,824,000	0.7	91%	9%
9/28/21	.....	70%	132,000	3,776,000	0.9	——	——
10/ 6/21	.....	70%	180,000	3,664,000	0.9	93%	7%

* One Holzknecht unit, skin distance.

NOTE:—During the first course of treatment each application of x-rays, consisting of HI S.D. at 12 inches' distance, was given to a different portion of the body, so that at the end of the course the entire cutaneous surface had been treated. During the second course most of the trunk was again treated. The same dosage was given, modified, however, by the use of a 1 mm. aluminum filter.

general was not so dense as in the reticular layer. There was considerable œdema and the papillæ were much prolonged, corresponding to the increased length of the pegs. The blood capillaries were dilated, frequently engorged with blood and often showed proliferation. Remnants of the collagenous tissue formed thin strands running vertically downward from the basal layer of the epiderm, to which they often seemed fused, and lost themselves in the thicker infiltration below. These strands showed an increased number of nuclei and were often paralleled by apparently newly forming capillaries.

In the papillary layer the predominating cells were of the small lymphoid type with round or irregular densely staining nuclei (Fig. 9). A thin, frazzled rim of protoplasm was occasionally demonstrable. A few larger cells of the fibroblastic or endothelioid variety were present and an occasional plasma cell was seen.

In the affected portion of the reticular layer the cells were massed promiscuously with no definite arrangement (Fig. 10). There was a granular intercellular substance with fine fibrils and occasional strands of coarser connective tissue. Round cells of the small lymphocytic type predominated in most fields. Many of the nuclei were quite irregular in shape and frequently had a shrivelled appearance. Besides these, there were numerous larger cells with nuclei varying in size up to the epithelioid type. These often predominated around the connective-tissue remnants. Oval, irregularly roundish, spindle and vesicular shapes were seen and occasionally kidney or horseshoe-shaped nuclei. The chromatin content varied from the finest reticulum to coarse structures with one or more nucleoli or chromatin clumps. Although most of these cells were apparently derived from the capillaries, connective-tissue remnants or the fixed cells, some of them may have been younger lymphoid cells or lymphoblasts. Our inability to demonstrate well defined individual cell protoplasm made it impossible to identify definitely cells of this character.

A few mitotic figures were found, but they were very rare.

No giant cells or eosinophiles were seen. Groups of plasma cells were frequently present at the lower border of the infiltration.

In the lower portion of the cutis the infiltration around the blood vessels and sweat glands was similar to that forming the dense band above, except that plasma cells were more numerous (Fig. 11). The majority of the small blood vessels and capillaries down into the fatty layer showed some degree of proliferation of their endothelium or perivascular tissue.

No sebaceous glands were seen, but occasionally one could find a well preserved hair follicle. The elastic tissue had for the most part disappeared from the densely infiltrated area. Small pigment deposits were fairly numerous, lying free or within some of the cells. They were not confined to any particular depth in the affected area.

2. *Papillomatous formation on the ankle.*—Corresponding to the clinical appearance one found here an extensive wart-like hypertrophy of the epidermis. The infiltration in the cutis was fairly dense and consisted almost entirely of small round cells. There were numerous vertical strands of richly cellular connective tissue and proliferating capillaries.

3. *Skin from thigh ten days after receiving H1 S. D. x-rays.*—The changes here were essentially the same as in the first preparation from the same area. There was not so much œdema in the papillary layer, however, and the difference in the density of infiltration in this layer and in the reticular layer was not so great. There was no apparent diminution in the extent of the infiltration or change in the appearance of the cells as a consequence of the x-ray treatment.

4. *X-ray dermatitis on buttock.*—Here was found a complete destruction of the epidermis with the usual manifestations of an acute inflammatory reaction in the papillary layer. The dense infiltration in the upper part of the reticular layer and around the deeper structures showed no apparent change or evidence of absorption.

Review of Literature.—According to Arndt,[1] only three cases of universal lymphadenosis of the skin, in which the hematologic and histologic study left no doubt as to the diagnosis, had been published before the report of his case in 1911. These cases were recorded by Riehl,[2] Linser,[3] and Rodler-Zipkin.[4] Since that time we have found only one other case which may be properly classified in this group. This was published in 1914 by Bernhard [5] and is Case 1 of a series of seven cases which he reported as instances of "Leukemia of the Skin." This case with our own makes a total of six cases and we have briefly outlined their principal characteristics in Chart II.

In a study of this chart it will be seen that all of the cases showed a blood picture suggestive of lymphatic leukemia. As has been noted by Arndt, Rodler-Zipkin's case differed somewhat from the usual type. Here the relative increase in the lymphoid cells was not very large and there was a greater proportion of large than of small lymphocytes. This patient's blood, however, was examined on the day of her death and the differential count was made after death. The author explains the large proportion of polymorphonuclear leukocytes by the existence of a sinus into the patient's knee-joint which had followed an injury some years before.

Other cases are recorded in the literature presenting similar universal skin eruptions with more or less implication of the lymph glands, liver and spleen, but in which nothing in the blood examination suggested leukemia. Such have been reported by Sweitzer,[6] Wechselmann,[7] Bernhardt [8] and Wise [9] as instances of an aleukemic leukemia or pseudoleukemia. Of interest in this connection are also the cases reported recently by Sequeira and Panton,[10] under the title "Lymphoblastic Erythrodermia," and two cases of an exfoliative erythrodermia published by Symmers,[11] one occurring in Hodgkin's disease and one in lymphatic leukosarcomatosis.

Comment

The case which we have recorded is a typical example of lymphatic leukemia irrespective of the skin condition. The dense infiltration of the cutis, however, with lymphoid elements makes certain that this tissue has also become involved in the leukemic process in a way similar to that in which the glands and some of the internal organs are more frequently affected in this disease.

The apparent rarity of this type of cutaneous involvement in lymphatic leukemia is probably due, in part at least, to insufficient blood studies in cases of this character. It is generally recognized that leukemia may go through aleukemic stages, in which the blood count is normal or varies little from the normal, so that some of the cases, at least, reported as instances of aleukemic leukemia or pseudoleukemia may belong to the true leukemias. The appeal of last resort, however, lies in the blood findings, and the correctness of a diagnosis, if unsupported by them, may be open to question. This would be especially true in the earlier stages of the disease, when the infiltration in the cutis was limited to perivascular areas or before the eruption had become generalized.

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[1] Dermat. Ztschr., 1911, XVIII, 1.

[2] Quoted from Arndt.

[3] Arch. f. Dermat. u. Syphilis, 1906, LXXX, 1.

[4] Virchows Arch., 1909, CXCVII, 135.

[5] Arch. f. Dermat. u. Syphilis, 1914, CXX, 17.

[6] Jour. Am. Med. Assn., 1906, **67**: 1511.

[7] Arch. f. Dermat. u. Syphilis, 1907, LXXXVII, 203.

[8] *Loc. cit.*

[9] Jour. Cut. Dis., 1917, XXXV, 669.

[10] Brit. Jour. Dermat., 1921, XXXIII, 391.

[11] Jour. Cut. Dis., 1919, XXXVII, 1.

Fig. 1.—Universal lymphatic leukemia of the skin.

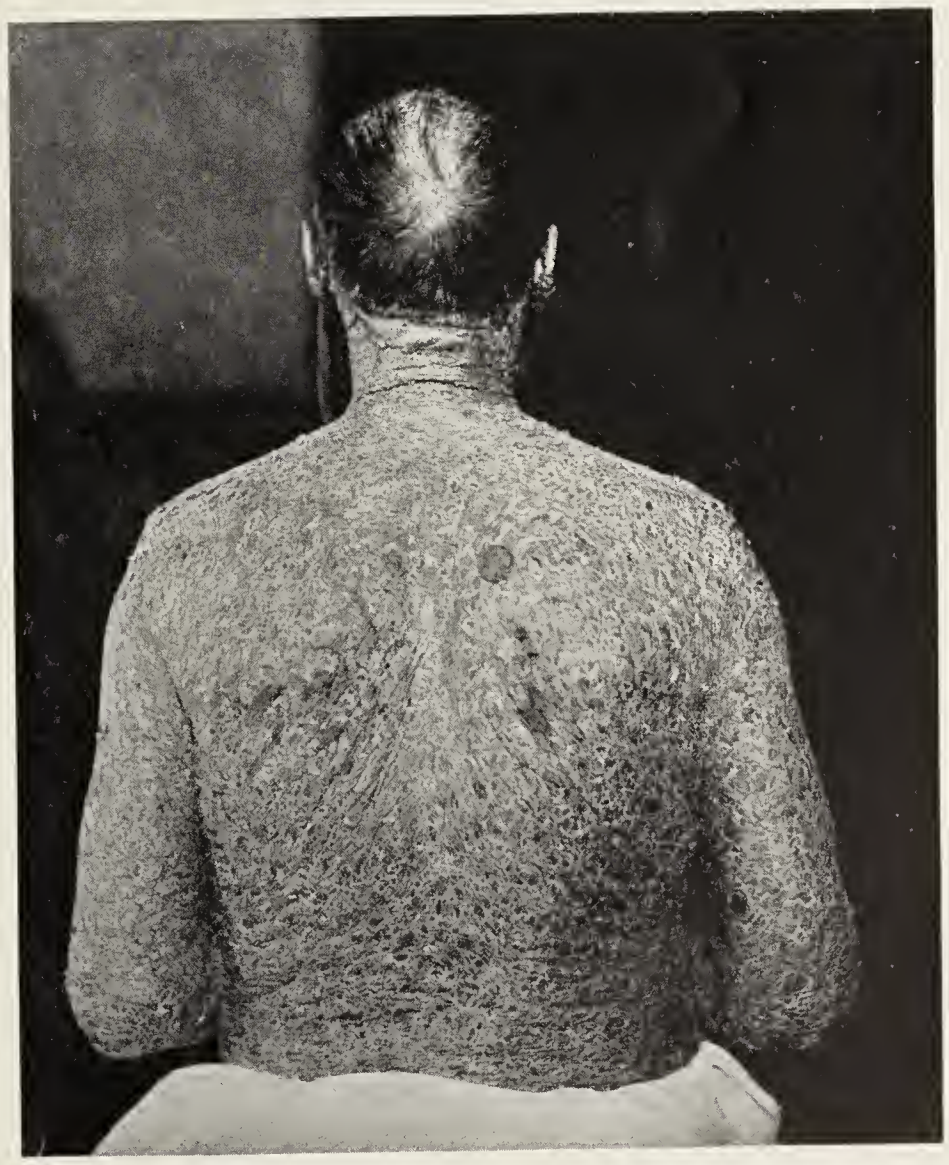

Fig. 2.—Back view of Fig. 1. (The small tumor on the right shoulder is a nevus.)

Fig. 3.—Shows papillomatous formation on ankles.

Fig. 4.—Extensive hyperkeratosis of soles.

Fig. 5.—Note changes in the nails and the intense infiltration of skin of fingers.

Fig. 6.—Low magnification of infiltrated portion of corium. Note invasion of epidermis by lymphocytes.

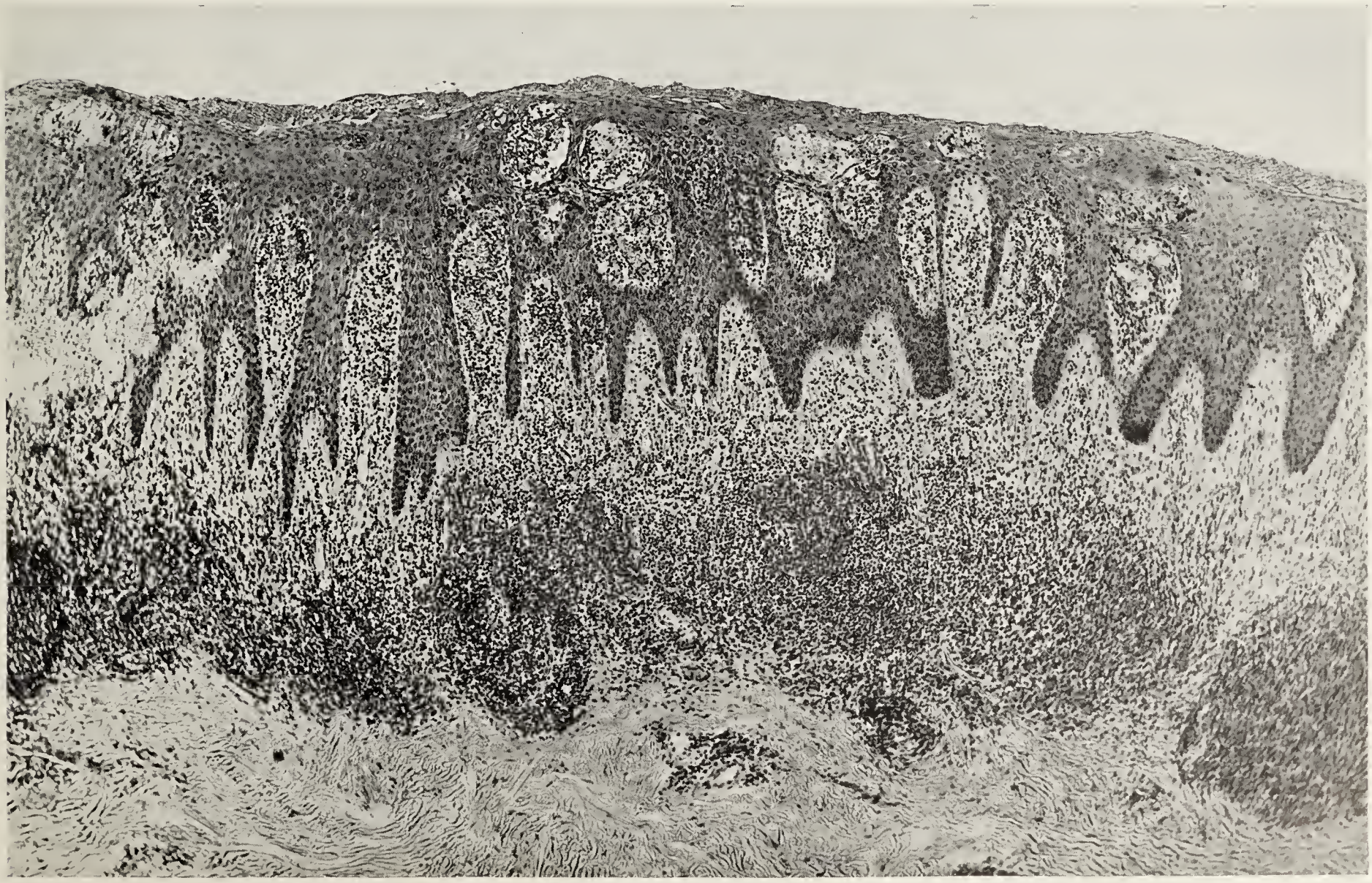

Fig. 7.—Similar to Fig. 6, but shows more destructive changes in epidermis.

Fig. 8.—Very low magnification of a section of the skin to show depth of the infiltration in the cutis.

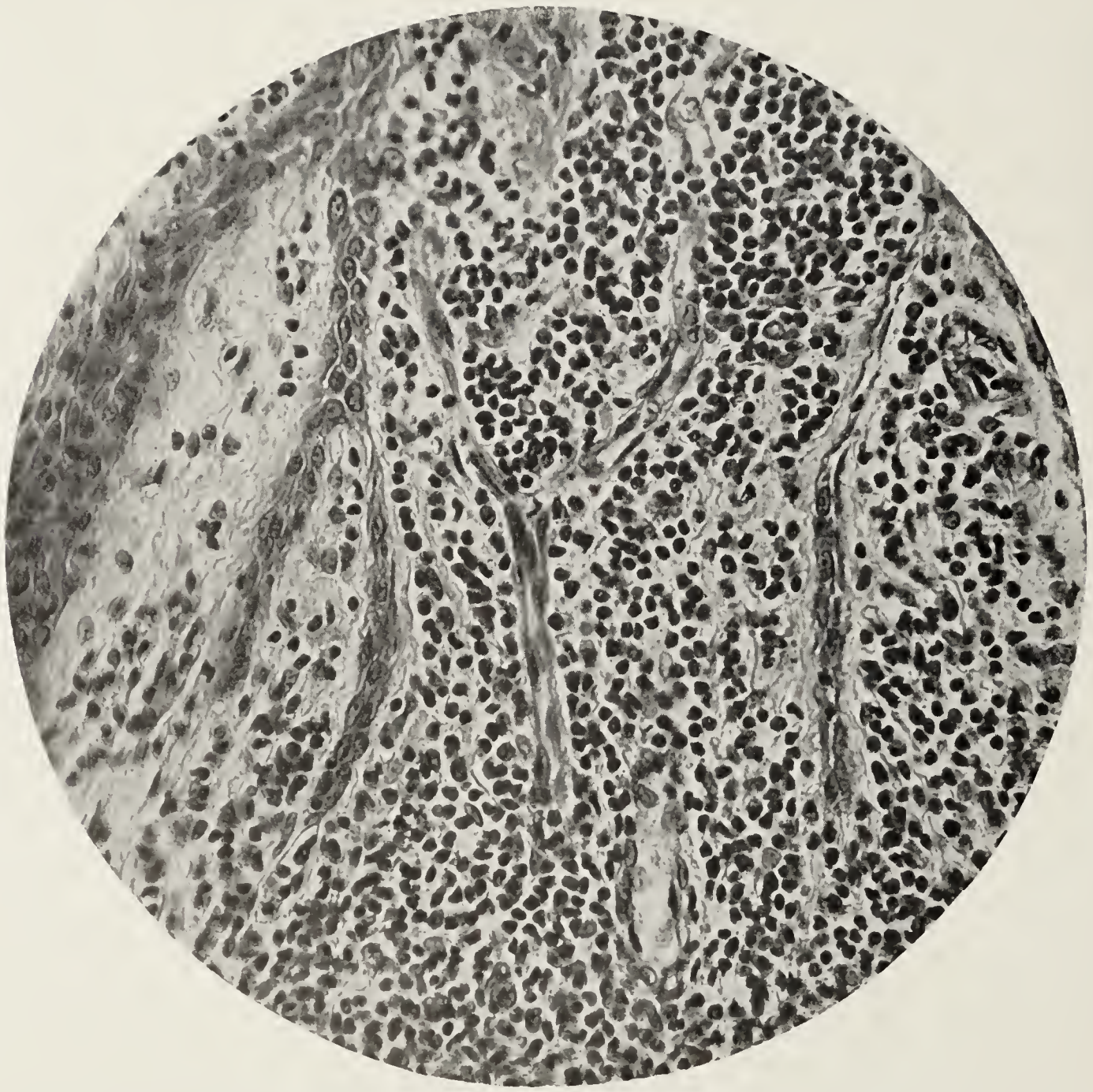

Fig. 9.—High magnification of a portion of the papillary layer. On the right and left are thin epidermal sprouts; in the center a Y-shaped capillary.

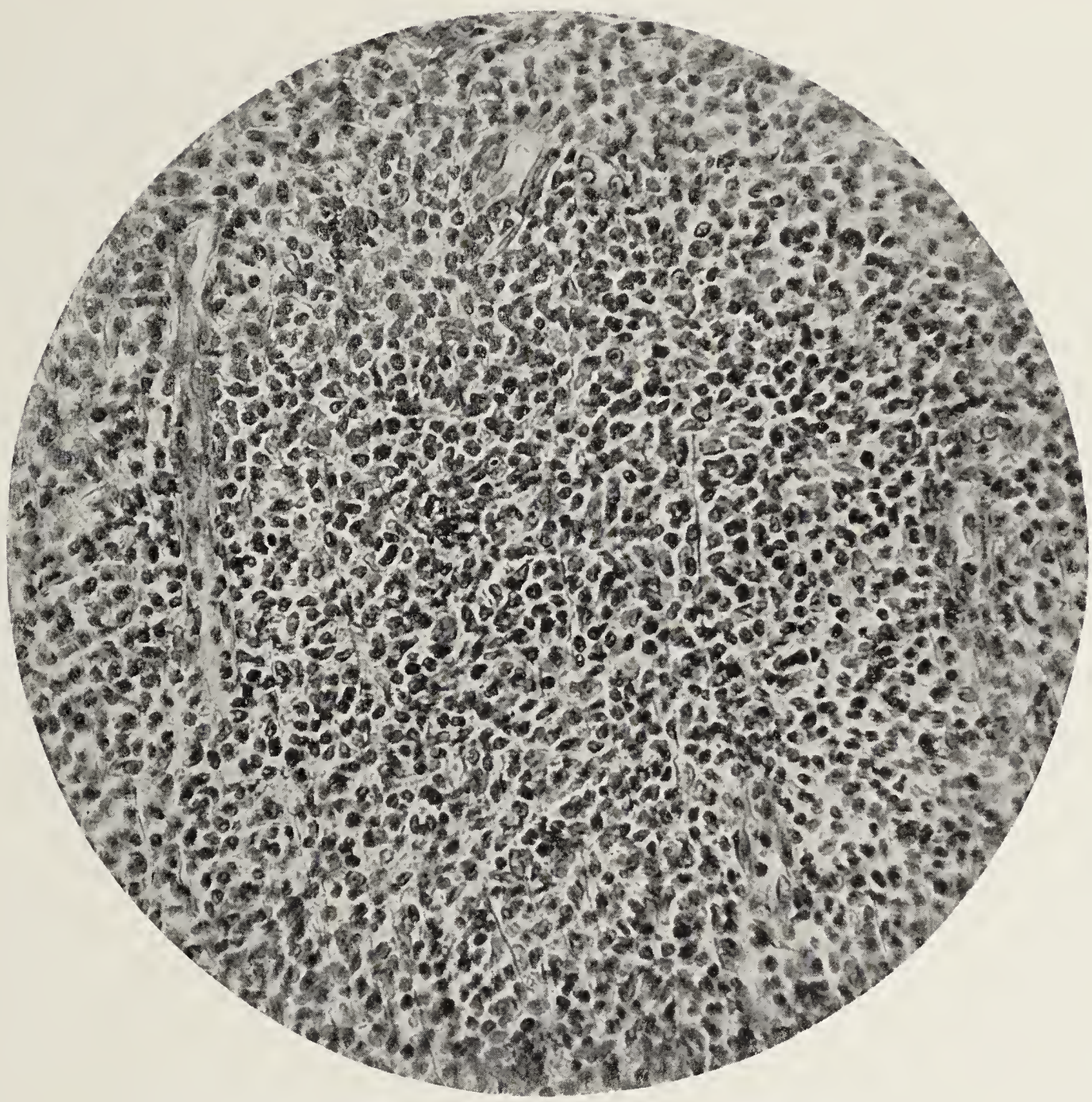

Fig. 10.—High magnification of infiltration in reticular layer.

Fig. 11.—Shows infiltration around sweat glands and blood vessels in lower portion of reticular layer.

CHART II.

Reported cases of universal lymphadenosis of the skin.

Case of	Sex	Age	Duration	Beginning	Character of eruption	Glands	Liver and spleen	Greatest white cell count	Percentage of lymphocytes in blood	Autopsy findings	Histology of skin
Riehl	F	57	4 yrs.	Eczematous itching patches on back.	Generalized reddening and swelling with thickening of skin of face, neck and inguinal regions. Surface generally dry with moderate scaling. Here and there moist areas.	Pea to apple size.	Distinctly enlarged.	Proportion of white cells to red cells as 1-24.		Characteristic changes of lymphatic leukemia.	Infiltration of variously sized round cells with large nuclei and scant protoplasm. Numerous eosinophiles.
Linser	M	58	1½ yrs.	Vesicular, reddish, itching eruption in bends of joints.	Generalized thickening and reddening of skin which was covered with scales. Excoriations over buttocks, skin bled easily.	Enlarged to size of apples.	Enlarged	47,000	94%		Dense infiltration in the cutis composed for the most part of small lymphocytes. A few mast cells; no eosinophiles or plasma cells.
Rodler-Zipkin	F	41	3 yrs. or more	Itching reddish patches.	Generalized diffuse reddening, scaling and thickening of skin. Dry and like parchment.	Markedly enlarged.	Enlarged	44,000	Large 28% Small 15%	Infiltration of liver and spleen with large lymphocytes.	Cutis densely infiltrated with large lymphocytes. Giant cells numerous. A few mast and plasma cells. No eosinophiles.
Arndt	M	55	8 mos.	Severe itching with generalized reddening and swelling of skin.	Generalized diffuse reddening and thickening of skin. Moderate scaling, moist areas here and there.	Enlarged to size of child's fist.	Not palpable.	800,000	78%	Leukemic changes in internal organs.	Dense lymphatic infiltration in cutis with large lymphocytes and lymphoblasts predominating. Giant cells present; also a few mast cells and eosinophiles.
Bernhardt	F	57	2½ yrs.	Reddish, scaly itching eruption on scalp.	Generalized thickening and reddening of the skin with abundant scale formation, areas of atrophy, nodules and warty formations.	Enlarged	Spleen enlarged.	54,000	Large 12% Small 72%		Dense infiltration of small lymphocytes in cutis. A few mast and eosinophile cells.
Ketron and Gay	M	63	10 mos.	Intense itching and reddening of legs.	Generalized thickening and reddening of skin, very profuse scaling. Skin bled easily, warty formations on ankles.	Size of English walnuts.	Spleen enlarged but not palpable.	184,000	Large 2% Small 90%		Dense small lymphocytic infiltration in cutis with moderate amount of fixed tissue cells. No eosinophiles. Numerous groups of plasma cells.

According to Arndt, the histological picture of this disease is characterized by a lymphocytic infiltration in the cutis, the large lymphocytes and lymphoblasts, however, predominating over the small lymphocytes. In this respect it is in contrast with the circumscribed lymphadenoses, in which the cells are almost wholly of the small lymphocytic type. In the universal form, also, numerous mitoses are found, and a characteristic zone free, or almost so, from infiltration is present in the papillary layer. Our histological findings vary considerably from those of Arndt. Practically no mitoses were found in our studies and the cell-free zone in the papillary layer was not present. Further, we have considered most of the infiltrating cells in the cutis as small lymphocytes, although some of the larger forms may have been large lymphocytes or lymphoblasts. We found it impossible to differentiate various degrees of development in the lymphoid series, if such had existed, where the cells were so densely packed together and when the protoplasm of the individual cells was not well defined. We believe that the cellular infiltration of the cutis in this disease is not necessarily confined to one lymphatic cell type or complex, but may vary, depending upon the age of the cells liberated from the blood stream and perhaps upon their further development in the tissues.

One of the most interesting points in the histology of our case was the extensive invasion of the epidermis by lymphoid cells. Here they were found scattered about diffusely or in cell-nests lying in the greatly prolonged pegs, in the rete, or between the lamellæ of the parakeratotic horny layer. If one considers the vast amount of scale formation and exfoliation present in this case one must realize that no inconsiderable quantity of lymphoid cells was gotten rid of in this manner.

Bernhardt's case is the only one of the six referred to in this report in which nodular lesions were associated with the universal lymphadenosis. This patient also had warty papules or formations on the skin, which were also present in several cases of pseudoleukemia cutis with more or less general involvement of the skin reported in the same communication. Lesions of this character were also present on the legs in our case.

Conclusions

1. A case of universal lymphatic leukemia of the skin is reported; the blood showed the characteristic findings of chronic lymphatic leukemia.

2. Our case is the sixth one of this unusual skin manifestation of lymphatic leukemia that apparently has been so far reported in the literature. Similar cases, however, have been recorded which are considered examples of aleukemic leukemia or pseudoleukemia in which the blood findings were normal or varied but little from the normal.

3. X-ray treatments to the skin brought about little improvement in our patient.

4. Our histological findings differed, in certain respects, from those which are considered by Arndt as characteristic of the disease. We believe that the cellular infiltration in the cutis is not necessarily limited, in all cases, to one cell type or complex, but may vary depending upon the age of the cells liberated from the blood stream and perhaps upon their further development in the tissues.

ASTHMA AND INFECTIONS OF THE ACCESSORY NASAL SINUSES:

A STUDY BASED ON 62 CASES

By Clyde A. Heatly, M. D. and S. J. Crowe, M. D.

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During the past decade, the more general aspects of asthma have been accorded increasing interest and thought; and the results of important experimental work have been to clarify our conception with regard to its fundamental nature and varying phases. It was Meltzer [1] who first pointed out the marked similarity between an asthmatic paroxysm and an anaphylactic shock, and suggested that the former, like the latter, might be due to exposure to a foreign protein to which the individual was hypersensitive. Since then, numerous workers have offered contributory evidence to this premise; so that Miller's [2] definition of asthma as "paroxysmal dyspnœa due to spasm of the bronchioles developed as a result of exposure to a foreign protein to which the individual is sensitized" may be accepted as a fair statement of our present attitude.

The purpose of this paper is not a discussion of these more fundamental principles of asthma; but rather an attempt to clarify our ideas with regard to a phase of the subject which has been the source of much interest and speculation ever since Voltolini's report from Vienna, in 1871, of a case of asthma cured by simple removal of a nasal polyp,—namely, the therapeutic possibilities in asthmatic states of operations on the nose and accessory nasal sinuses.

That pathological conditions in the nose and accessory sinuses may have an important bearing upon cases of bronchial asthma has been repeatedly emphasized for years by many writers, notably Schäfer, Porter, Fränkel, Schmiegelow, and others. Furthermore, the presence of points on the mucous membranes of the nose, pharynx, or

bronchi (so-called "asthmogenic points"), the stimulation of which, in susceptible subjects, may provoke bronchial spasm with typical asthmatic paroxysm, has received repeated confirmation—notably in the experimental work of Brodie,[3] Dixon and Sewall on the innervation of the bronchial musculature. We are not here attempting to do more than to restate a premise which, we believe, is widely and justly held by clinicians—that pathological conditions in the nose and accessory nasal sinuses bear some relationship to clinical asthma.

The aim of this study is to attempt to conclude from a review of a series of 62 cases which have come under our care at the Johns Hopkins Hospital: (1) The value of operations on the nose and accessory sinuses as part of a therapeutic programme in asthmatic patients presenting pathological conditions in that region; and (2) the type of operation (whether *simple* or *radical*) which in our experience has proved most beneficial. That any such operative procedure must be properly indicated and part of a more general therapy (*i.e.* specific and nonspecific protein vaccines, drugs and supportive measures in appropriate cases) is, of course, of fundamental importance. There is no place today for simple routine cauterization of, or electrolysis to, certain points on the nasal mucosa; or, in fact, for any procedure which does not take into consideration the exact conditions presented by the individual case.

General Data.—The following statistics are based on a series of 62 patients who were examined and operated on in the Laryngological Clinic of the Johns Hopkins Hospital. The series includes both private and ward patients. Many of them were referred from the general medical clinic; and all of them, prior to operation, had been submitted to general medical studies, so that mere cases of dyspnœa not dependent upon bronchial spasm—such as dyspnœa due to renal or cardiac diseases—have not been included. Unfortunately, only slightly over one-sixth of our series were subjected to complete preliminary asthmogenic tests, the smallness of the proportion being due to the fact that we desired to incorporate the cases of many patients whom we had followed for years, but who were in the hospital before such tests had become a matter of routine.

It has been repeatedly observed in statistics based on large series of cases that the majority of asthmatics date the onset of their symptoms from early life. Thus Salter [4] in a series of 225 cases found that the first symptoms appeared in the first decade in 31 per cent. The age of incidence in our own series is noted in the following table:

TABLE I.

Age of incidence	Number of cases	Per cent
1—10 yrs.	15	24.1
10—20	12	19.45
20—30	12	19.45
30—40	8	12.9
40—50	10	16.1
50—60	5	8.0
60—70	0	0
Totals	62	100

The definite tendency to asthma in families, which has been emphasized by Longcope,[5] Cooke,[6] Vanderveer, and others, is also evident in our series, although in somewhat a smaller percentage of cases. Thus, a positive history is given by 8 patients (12.9%), this relatively small incidence being probably due to failure on the part of certain house officers to inquire definitely concerning this point.

The somewhat increased frequency of asthma among members of the male sex which is evident in Salter's [7] records is practically duplicated in our own series. Thus, 41 (66.1%) of our patients were males and 21 (33.%) were females.

All cases reported, save one, occurred in members of the white race; the one exception being in a negro. This is probably due to the large proportion of private cases in the series.

No attempt has been made to divide our cases into so-called "true asthma" and "asthmatic bronchitis" (cf. Walker [8]). Such a division would be manifestly impossible from the histories alone in a series in which complete asthmogenic tests had not been routinely carried out. We feel, however, that this division is at best difficult and often unsatisfactory; and that it is by no means essential to the interpretation of such data as we shall present.

We noted two interesting points in symptomatology: (1) the frequency of catarrhal symptoms and head colds (present in 60 of our cases)—an observation which has been emphasized by Sherman; and (2) the relative infrequency of headaches. Thus, of 62 patients, only 14 admitted any tendency to headaches; and in only 2 of these were headaches really frequent and troublesome. This fact is the more surprising when one considers the frequency of sinus infection in this series. The common findings at operation of polypi or polypoid hypertrophy of sinus mucous membranes associated with little or no free pus may offer an explanation for this, since headaches are more frequent in cases of sinusitis with pus under tension.

Only one patient in the series had an associated pulmonary tuberculosis (inactive), which seems to bear out

the general opinion that there is no greater tendency to tuberculosis in asthma than in any other chronic infection.

Local Clinical Findings.—We are not at present prepared to offer any statistics concerning the frequency of abnormalities in the nose and accessory sinuses in asthmatics. This subject has been investigated and estimated with wide variations by other writers—Lublinski [9] (29%), Scheck (64%), Matthews (88%). Many of these reports are without doubt misleading and based on abnormalities too slight to deserve attention. They do not concern us in our present study.

The frequency, however, of pathological conditions encountered in the regional examination has been investigated. The most common of these in our patients was the nasal polyp, one or more being found in 38 (61%) of our series. This frequency of nasal polypi in asthmatics has been noted in other series, such as those reported by Schmieglow,[9] Francis, Matthews, and others.

The ethmoids and antra were the sinuses most frequently found to be infected. Infection of the frontals and sphenoids was relatively uncommon. A diagnosis of pansinusitis was confirmed in 7 cases (11%). Obstructive deviation of the septum (including spurs), hypertrophied membranes on turbinates, chronically infected tonsils and infected adenoids were also found to exist in many cases. Various combinations of these conditions were often present in the same individual. (See Table II.)

TABLE II.

Pathological findings	Cases
Nasal polypi	38
Sinusitis (chronic)	
Infected ethmoids	20
Infected antra	19
Infected frontals	2
Infected sphenoids	4
Pansinusitis	7
Obstructive septal deviations	17
Obstructive hypertrophied turbinates	25
Inferior	14
Middle	11
Tonsillitis, chronic; infected adenoids	12
Infected adenoids alone	3

Operative Results.—It has been justly stated by Brown [9] that, strictly speaking, "an actual permanent cure in asthma is rarely obtained." There is only one patient in our series who, writing after three years, is enthusiastic enough to describe himself as "cured." Nevertheless, those who are familiar with asthmatics will agree that any "improvement" is decidedly worth while.

To list improvement is one thing; to establish the reason for cure is quite another; and in a condition, like asthma, where many factors are concerned, it is difficult correctly to evaluate any single therapeutic measure, operation included. We recognize this clearly, and realize it to be the weakness of any statistics dealing with the results of the treatment of asthma. Nevertheless, such statistics must be attempted if we are to make any real progress in our knowledge concerning therapeutic possibilities in asthma.

We have considered our series from the standpoint of improvement or unimprovement. Further subdivisions are difficult and tend to inaccuracy. We have, furthermore, noted the length of time that elapsed from the time of operation to the date on which the note concerning result was made. There is a definite number of patients in whom after a varying period of often very marked improvement, the asthmatic attacks recur. These are listed as "temporarily improved cases" and the length of period of relief is noted. Those patients, totally unhelped, are listed as "unimproved" (Table III). We have attempted, so far as possible, to omit patients in whom other therapeutic factors were simultaneously in action.

TABLE III.

Post-operative Time period	Improved	Unimproved	Recurrence after Temporary improvement
6 mos.	14		8
1 yr.	9		2
2 yrs.	10 (1 died)		1
3 yrs.	7		2
4 yrs.	3 (1 died)	9	1
5 yrs.	1		
6 yrs.	7		
7 yrs.	0		
8 yrs.	1		
9 yrs.	1		
Totals	53 cases	9 cases	14 cases
	Total 62 cases		

One striking thing noted in this series is the number of cases in which recurrence of symptoms took place after a varying period of improvement. Some of these patients, returning for re-examination, showed evidence of a recurrence of the intranasal infection (pus or polypi), thus offering a possible explanation for a recrudescence of symptoms. Many were living at distant points and no re-examination was possible.

It has been shown by Walker [8] and other workers that the age of onset of asthmatic symptoms bears an important relationship to sensitivity; that the earlier in life the appearance of symptoms, the greater the possibility of a specific sensitization basis; and that, vice versa, as age at onset increases, the incidence of sensitization decreases. With this in mind we attempted an analysis of our series from the standpoint of the influence of age at onset on the operative result. So far as we could deter-

mine, the age at onset bore no definite relationship to the operative result.

Similarly, mere duration of symptoms alone did not seem to influence the progress. In cases, however, whether of long or short duration, showing clinically a persistent and firmly rooted bronchitis, our operative results were frequently poor; the impression being that the persisting bronchitis was an infection sufficient to offset any possible benefit from operation. On the other hand, some cases presenting less severe signs of bronchitis were favorably influenced. The degree of bronchitis, rather than mere duration or age at onset, seemed in our series to be an important factor in prognosis.

As has already been stated, our desire to review a series of cases of some years' standing necessarily reduced the number of cases on which complete asthmogenic tests have been done. The necessity of complete sensitivity tests in asthmatics as a preliminary to any therapeutic procedure is now as widely accepted as it is known. Any therapeutic programme which fails to recognize this must obviously prove inadequate.

Complete asthmogenic tests were performed in 13 cases of our series (Table IV). Of these, the majority proved non-sensitive and, of these, the majority likewise showed improvement. It is obvious that in cases giving a positive cutaneous reaction, operative procedure must, if indicated at all, go hand in hand with specific protein treatment.

Type of Operation.—The final object of investigation in our series concerned the type of operation (*i. e.* whether simple or radical) which in our experience had proved most effective, as judged by operative results. One thing seemed very clear—that, while in occasional patients excellent therapeutic results were obtained by so simple an operation as removal of nasal polypi, in the vast majority of cases such simple procedures proved either very transient in their effect or utterly useless. Patient after patient in our series came to us after having submitted to many such measures. One patient had had nasal polypi removed on seventeen different occasions without relief. His symptoms improved very definitely after a radical operation which aimed to cure the sinus infection, and he has remained improved for four years. There are conspicuous exceptions in our own series, but this conclusion seems justifiable—that the best results can be expected only in those patients in whom thorough eradication of the local infection has been conscientiously attempted. The return of asthmatic symptoms in certain of our patients who showed clinically a return of intranasal infection seems additional evidence in favor of this conclusion. The statement of Matthews [10] that "relief of asthmatic symptoms corresponds in degree to the extent to which pathological conditions in the nasal sinuses and nasopharynx have been improved" seems to indicate similar experience in other clinics.

TABLE IV.

Positive reaction: (2 cases)		
Time	Improved	Unimproved
Seven months	Case of S. B.—aged 15—Asthma for 12 years. Reacted to rag weed and timothy. First seen in October, 1922. No serum treatment begun until April, 1923—Six months after operation (ethmoids and antra). No attacks since operation.	Case of A. G.—43 yrs. old. Asthma for 15 years. Had bad bronchitis. Reaction to timothy and June grass. Not helped by pollen treatments. Unimproved by operation.

Negative reaction: (11 cases)		1 case
Time	Cases	
6 mos.	6 (3)*	(A man of 23 with asthma for two years. All tests negative. Operation consisted in simple removal of septal spur. No polypi present. No improvement noted.)
1 yr.	3	
2 yrs.	1	
3 yrs.	1	
4 yrs.	0	
Total	11	

(3)* Three cases of recurrence after temporary improvement

Relationship.—The actual relationship of pathological conditions in the nose and accessory nasal sinuses to asthmatic states is a matter of interesting speculation, but beyond the real province of this paper. That an infected area in the upper respiratory tract acting as a source of infection to the lower tract, especially during sleep, might be sufficient to provoke or perpetuate asthmatic symptoms in an individual with such tendencies is not difficult to conceive. On the other hand, Auer's [11] recent experimental work in local autoinoculation, which seems to suggest that a sensitized organism under certain conditions [(1) presence of circulating antigen and (2) local accumulation of this antigen *in a tissue showing some degree of inflammation*] can reinfect itself locally, causing a local anaphylactic state—may supply the key to the true causal relationship.

CONCLUSION

Certain things at least are very clear—that indiscriminate operations on the nose and accessory nasal sinuses of asthmatics are to be condemned; that, if attempted, they must be properly indicated and radical in the sense that they aim to eradicate all existing regional infection. Operative measures, so attempted, will improve a very definite proportion of asthmatic cases. They should, however, always be undertaken as a part of a general therapeutic programme.

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ON THE DISSEMINATION OF HEMOLYTIC STREPTOCOCCI AMONG A GROUP OF HEALTHY PEOPLE*

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During the course of observations on acute streptococcic infection (tonsillitis) in a group of people under close bacteriological and clinical control, it seemed desirable to study some of the broader phases of streptococcus parasitism. The problem, in brief, centered on the significance of the carrier and on the laws governing the spread of bacteria from one person to another, with colonization and the production of secondary carrier states.

There are numerous observations on record which indicate that the percentage of carriers of one or another potentially pathogenic micro-organism may remain quite constant in a community over long periods of time. It is known, for example, that despite the presence of about 2 per cent of carriers of virulent diphtheria bacilli in large groups of people who have been examined in this regard, there may be no development among them of fresh carriers nor of any cases of clinical diphtheria.[1] It becomes clear, then, that the mere presence of a source of bacteria, together with opportunities for contact, is not necessarily adequate to lead to extensive spread of an organism throughout a community, with colonization, growth and subsequent production of disease.

In the present work it has been pointed out that among a group of nearly two hundred healthy young women there were found about 41 per cent of carriers of beta hemolytic streptococci, and that such carriage was essentially dependent on a focal tonsillar infection.[2] Furthermore, despite the large number of sources of infection no new carriers could be shown to arise by contact, although certain instances of sporadic streptococcus infection (tonsillitis) did occur and were followed by persistence of streptococci. In other words, under the conditions of the present experiment beta hemolytic streptococcus parasitism appeared to be remarkably stable and there was no tendency to further spread of the organisms through the community.

On the other hand, there are many observations in the literature which suggest that alterations take place from time to time in the distribution of pathogenic bacteria in the throats of healthy people, and that such alterations bear some relation to the spread of clinical infection. It has been amply demonstrated, for example, that large outbreaks of epidemic meningitis may be preceded by a great rise in the carrier rate—even up to 20%—among the group later to be affected,[3] and we have shown similar variations in the parasitism of influenza bacilli,[4] although in this case the phenomenon is less distinctly related to the production of disease. Epidemiologists have considered this matter, and Topley [5] especially raises the question whether certain types of infection are not preceded by a "saprophytic spread" of the organisms among the healthy and as yet unaffected population. Topley later [6] subjected the point to experimental study by observing the development of an epidemic among a group of mice, some of which had been infected with bacilli of the enteritidis group. He found that during the pre-epidemic stage single deaths or small groups of deaths due to the specific infection studied occurred at considerable intervals before the rise of the main epidemic wave, affording a warning that such a wave was at hand, and that at the time when the first death occurred the parasite could already be recovered from the tissues of many of the other inhabitants of the cage, although they were apparently in normal health. To describe the accumulation of circumstances which seems to be necessary before an epidemic wave can be propagated, Topley, following Peters, uses the term *epidemic potential,* and concludes that when this potential has reached, during the pre-epidemic phase, some critical value, a wave of specific disease will be propagated. It is, of course, further conceivable that such an epidemic potential may never reach

*This is the eighth of a series of papers on Streptococcus Infection with Special reference to Acute Tonsillitis.

an adequate point, and that conditions may resolve without an actual extensive outbreak of disease.

From the start of the present work we had been on the look-out for evidence of any such saprophytic spread, but no alteration in the extent or kind of streptococcus parasitism was demonstrated in the experimental group during the months of September and October, 1922, even after cases of acute tonsillitis had begun to occur. During January, 1923, however, there was a distinct increase in the number of tonsillitis cases and there was also an epidemic of mild but definite influenza. Nearly everyone in the community was at some time affected, and cough was almost universal. Conditions seemed ideal, therefore, for the spread of bacteria, and further observations were undertaken at this time to determine whether any upset in streptococcus parasitism had taken place.

METHODS

The present work concerns itself only with hemolytic streptococci. The primary differentiation was made by appearance on the standard poured blood-agar plate, according to the method of Browth.[7] It may be recalled that several types of streptococcus are distinguishable on a basis of the degree and character of the hemolysis produced:

Beta (β) *type.*—A grey bi-convex or disk-like colony surrounded by a complete and clearly defined zone of hemolysis, 2 to 4 mm. in diameter. There is no greenish or yellowish discoloration of the medium, and on microscopic examination no intact cells remain in the hemolyzed zone or about the colony.

Alpha prime (α^1) *type.*—This type is indistinguishable from the beta group except in so far as the deep colonies "appear somewhat hazy and ill defined within the hemolyzed zone." "Under the microscope the reason for this haziness is apparent; a few corpuscles are seen to remain throughout the zone, but are most numerous next to the colony." On the surface of the plate these organisms may be indistinguishable from the beta type.

Alpha (α) *type.*—This is the common green-producing variety of streptococcus with slight clearing about the colony but no real hemolysis.

Gamma (γ) *type.*—The indifferent or "grey" streptococcus, which produces neither greenish discoloration nor hemolysis.

In a study of approximately one thousand cultures of hemolytic streptococci, it was possible absolutely to confirm Brown's observations as to the reliability of differentiation of strains in the standard poured blood-agar plate. The beta type is always distinct; there is never any doubt in the mind of the examiner as to its definition, and in our experience its type characteristics have invariably been preserved even after prolonged and repeated subculture. Conversely, the alpha and gamma types will never be confused with real hemolytic streptococci. The alpha prime type, on the other hand, from the standpoint of the clinical bacteriologist, deserves the most careful consideration, because mistakes in interpretation may lead to very erroneous conclusions as to the etiology of infection and the spread of disease. Unless the colonies are studied with the greatest care with the aid of the low power of the microscope, and unless poured plates and not surface cultures are used, these organisms are sure to be confused with the real beta types. And yet the significance of the two seems quite distinct. On subculture and by biological tests they turn out to be different, and while the real beta type is frequently concerned with disease, the alpha prime types are apparently non-pathogenic. We have never recovered from a case of tonsillitis, erysipelas, scarlet fever or other acute streptococcus infections a strain which did not have typical and undoubted beta type characteristics. In any epidemiological work, then, the two varieties which resemble each other so closely must be sharply distinguished. The importance of this point will be brought out in the work reported below.

The cultures were all made by the method previously described.[2] The swabs from various areas in the throat were diluted in broth, and 5% human blood-agar plates were poured with various dilutions.

EFFECT OF INFLUENZA ON STREPTOCOCCUS HEMOLYTICUS PARASITISM

During the influenza pandemic of 1918-19 it was notable that hemolytic streptococcus was widely disseminated. Furthermore, the incidence of streptococcic complications, especially broncho-pneumonia, was high and many of the deaths were attributable to this cause. During January and February, 1923, influenza became epidemic in Baltimore, and twenty-eight members of the present experimental group of two hundred students fell ill. However, there was not a single instance of streptococcus complication among these people. It seemed of interest, therefore, to study the dissemination of hemolytic streptococci at this time. Between January 24th and February 1st, at the height of the epidemic, throat cultures were taken in fifteen unselected cases. In a few of these people control cultures had previously been made. The results of the cultures are shown in Table I. It appears that real beta hemolytic streptococci were recovered from one person who had previously been shown to be a chronic carrier, and that from two others a few colonies of the alpha prime type were cultivated. The remainder yielded no hemolytic streptococci of any sort.

These findings are in harmony with the clinical events and indicate no alteration of streptococcus parasitism as previously defined.

It next seemed desirable to look for saprophytic spread of hemolytic streptococcus in a more systematic way. In order to eliminate confusion resulting from chronic tonsil

TABLE I.

Throat cultures for hemolytic streptococcus in influenza cases.

Name	Onset of influenza	Culture		Remarks
		Date	No. of hemolytic strept. per plate	
Cr.	Jan. 23	Jan. 24	0	
Br.	Jan. 23	Jan. 24	0	Cult. 9/7/22 Negative
Bru. ...	Jan. 20	Jan. 24 Feb. 1	0 0	
Fl.	Jan. 24	Jan. 26	0	
Co.	Jan. 23	Jan. 25	0	
Ca.	Jan. 23	Jan. 26	0	
Ro.	Jan. 25	Jan. 29	0	
Ma.	Jan. 27	Feb. 3	0	Cult. 9/9/22 Negative
Wo. ...	Jan. 26	Jan. 29	0	
Bo.	Jan. 26	Jan. 29 Feb. 1	0 2 cols. (a^1)	
Du.	Jan. 23	Jan. 29	0	
Cu.	Jan. 23	Jan. 29 Feb. 1	0 0	
Cou. ...	Jan. 27	Jan. 30	1% (a^1)	Cult. 9/20/22 50% β
Sm.	Feb. 1	Feb. 3	Many (β)	Cult. 9/26/22 Many β
St.	Feb. 1	Feb. 3	0	

carriers, thirty-three subjects were studied whose tonsils had been removed. They represented a random sampling of the whole group. In all of them control cultures had been made several months previously, in the late summer, at a time when streptococcus disease and acute respiratory infection were practically absent from the community. Between January 30th and February 7, 1923, these women were re-cultured, to discover, if possible, the development of any general and free growth of hemolytic streptococci on the mucous membranes of the throat. As may be seen from Table II (which is summarized in Table III), the control cultures had shown hemolytic streptococci in only six of this group and then only in small numbers, save in one instance. The re-cultures during the winter, on the other hand, showed a most strikingly different picture. Plate after plate (see Table II) was seeded with markedly hemolytic streptococci which at first glance seemed to be of the real beta type; but on careful study they were found with one exception to fall in the alpha prime group. The differentiation was made by macroscopic and microscopic study, which showed accumulation of unhemolyzed cells about the colony, and by the biological reactions of subcultures (fermentation, acid endpoint, agglutination). These reactions will be discussed in detail in another place. None of the organisms examined fell into the usual group of pathogenic human strains.

It appears, then, that a wide dissemination of hemolytic streptococci similar to, but distinguishable from, the definitely pathogenic type had taken place on the free mucous membranes of a group of healthy people,—a phenomenon which checked perfectly with the clinical facts. There was at the time no noteworthy accession of streptococcus disease in the community, as would have been inevitable, we believe, had a spread of real beta streptococci occurred.

Discussion

The phenomenon described above consists essentially of a wide dissemination among a group of people of organisms not members of the normal flora of the throat and also, as far as we know, not regular disease producers. No clinical phenomena could be related to the spread. Similar observations have been made in connection with other bacteria. Gordon [8] discusses the variations in distribution of type IV pneumococci in healthy people and we have described fluctuations in distribution of the so-called hemolytic influenza bacillus.[9] The theoretical aspects of the matter were discussed at that time.

It is of interest, therefore, to add another instance of such "saprophytic spread." In the present case, however, the point of greatest importance lies in the close similarity of the bacteria concerned to the true beta or disease-producing type of hemolytic streptococcus. It seems worth while to draw attention to the fact that epidemiological as well as isolated clinical bacteriological observations may be misinterpreted, unless care is exercised in differentiating the beta type organisms from the superficially similar alpha prime types. In the presence of clinical infection of the upper air passages, for example, recovery of the latter organism in almost pure culture might readily lead to etiological conclusions which, as we have shown above, are quite unwarranted.

Conclusions

1. Attention is called to the necessity of differentiating in clinical bacteriology between hemolytic streptococci of the true disease-producing or beta type and the very similar but essentially non-pathogenic alpha prime type (Brown).

2. In a repeated bacteriological survey of a closely controlled group of people, at various times of the year, no evidence was obtained of any alteration in the stable type of parasitism of the beta type of streptococcus.

3. This finding corresponded to the clinical absence of epidemic streptococcus disease.

4. Influenza was not associated with any spread of pathogenic types of hemolytic streptococci, nor were there any complications due to streptococcic infection in the present epidemic.

TABLE II.

Repeated cultures on a group of healthy people for presence of hemolytic streptococcus.

Case No.	Fall Series (1922)			Winter Series (1923)		
	Date	Pharynx	Tonsil fossae	Date	Pharynx	Tonsil fossae
4	Sept. 7	0	0	Jan. 30	5% (a^1)*	0
7	Sept. 8	0	0	Feb. 5	1% (a^1)	1% (a^1)
22	Sept. 15	0	0	Feb. 5	Few (a^1)	Few (a^1)
	Sept. 26	0	0			
23	Sept. 15	0	0	Feb. 5	20% (a^1)	20% (a^1)
36	Sept. 15	0	0	Jan. 30	0	0
37	Sept. 15	Few (β)	0	Jan. 30	0	0
39	Sept. 15	0	0	Feb. 7	0	Few (a^1)
41	Sept. 15	0	0	Feb. 7	10% (a^1)	10% (a^1)
43	Sept. 16	0	0	Jan. 30	2 cols. (β)	1 col. (β)
44	Sept. 16	0	0	Feb. 5	0	Many (a^1)
51	Sept. 18	Few (β)	Few (β)	Feb. 7	10% (a^1) No β	1% (a^1) No β
70	Sept. 22	0	0	Feb. 5	3% (a^1)	3% (a^1)
75	Sept. 22	0	0	Feb. 7	1% (a^1)	1% (a^1)
78	Sept. 22	0	1 col. (a^1)	Feb. 5	Few (a^1)	Few (a^1)
79	Sept. 22	1 col. (a^1)	10% (a^1)	Feb. 5	1% (a^1)	1% (a^1)
82	Sept. 22	0	0	Feb. 5	Few (a^1)	Few (a^1)
94	Sept. 25	0	0	Jan. 26	0	0
95	Sept. 25	0	0	Feb. 7	Few (a^1)	Few (a^1)
101	Sept. 27	1 col. (a^1)	0	Feb. 7	90% (a^1)	Many (a^1)
106	Sept. 27	0	0	Jan. 30	0	0
107	Sept. 27	0	Few (a^1)	Feb. 7	1% (a^1)	1% (a^1)
121	Oct. 9	0	0	Feb. 5	Few (a^1)	10% (a^1)
122	Oct. 9	0	0	Feb. 7	0	1% (a^1)
133	Oct. 11	0	0	Jan. 30	0	25 cols. (a^1)
140	Oct. 11	0	0	Feb. 5	Few (a^1)	Few (a^1)
145	Oct. 11	0	0	Jan. 30	Few (a^1)	Few (a^1)
152	Oct. 13	0	0	Feb. 7	50% (a^1)	Few (a^1)
160	Oct. 16	0	0	Feb. 5	Few (a^1)	Few (a^1)
163	Oct. 16	0	0	Jan. 30	1% (a^1)	Few (a^1)
168	Oct. 16	0	0	Feb. 5	10% (a^1)	10% (a^1)
182	Oct. 20	0	0	Feb. 7	0	0
187	Oct. 20	0	0	Jan. 30	0	0

* Number of colonies per plate.

TABLE III.

Summary of Table II.

Total in group	Fall Series		Winter Series	
	Positive (a^1)		Positive (a^1)	
	Number	Per cent	Number	Per cent
32	4	12.5	25	80.0

5. On the other hand, a wide distribution of alpha prime streptococci took place throughout the group.

6. The significance of this phenomenon with special reference to possible clinical misinterpretation is discussed.

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NOTE ON THE PHAGOCYTIC ACTIVITY OF HEMAL GLANDS IN THE SHEEP

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Introduction

The hemal glands have been the subject of numerous careful morphological investigations, but, in spite of this, little unanimity of opinion exists up to the present day as to the nature of these organs. Some observers believe that they are organs *sui generis* arising from independent "Anlagen," while others think that they are only modified lymph-nodes with all transitions existing between nodes without lymphatics and those with lymphatics. Opinion is also at variance as to their occurrence in different animals.

Nearly all the previous observations upon hemal nodes have been made upon dead animals in which colored fluids have been in many instances injected into the blood-vessels or lymphatics, or directly into the nodes themselves. Direct injections into nodes Arthur Meyer introduced as a means of determining whether a node possesses only blood-vessels, or lymphatic connections as well, hence, whether it is a hemal gland or lymph-node. These methods of post-mortem injection are valuable in investigating the problems of vascular and lymphatic supply of the nodes and offer considerable possibility for enlarging further our knowledge of the hemal gland.

We decided, however, to investigate the hemal node from an angle from which it has been very little approached, namely, from the standpoint of its functional activity towards colloidal sols or suspensions introduced into the living animal. It is hardly necessary to point out that much valuable information has been gleaned regarding the activity of the liver, spleen, lungs and other organs by this experimental method, so that it holds out promise to do likewise for the hemal node.

Mention has been made by several writers of the staining reaction of the hemal nodes in vitally stained animals. Thus Goldmann ('09) remarks upon the hemal nodes in vitally stained rats. He states that pyrrhol blue is stored in the form of numerous tiny granules in the cytoplasm of the reticular cells that occur in association with the reticular network of fibers throughout the glands. He observed that the vitally stained reticular cells may detach themselves from the fibers and become free in the sinuses.

The only criticism of Goldmann's observation upon hemal nodes is that it can be questioned whether in the rat one is actually dealing with hemal nodes and not lymph-nodes. Goldmann rests his assumption upon the statements of Vincent, Harrison, and Weidenreich that the rat possesses hemal nodes. Weidenreich himself, however, states that he considers the structures in question as only transitions between lymph glands and the hemal nodes, because he finds that they contain lymphatic sinuses in connection with afferent and efferent lymphatics as well as sinuses in the center of the glands which he believes are connected with blood-vessels only. More recently Meyer ('14) stated that he failed to find hemal nodes at all in the rat. It remains therefore a moot question whether the rat possesses hemal nodes, and consequently we must wait for the settlement of this problem before Goldmann's observations upon the vital staining of hemal nodes can be accepted.

Evans ('15) speaks of the behavior of hemal nodes towards vital dyes in mammals. He says "The lymphatic sinuses of lymph glands and the venous sinuses of hemal glands are lined with endothelial cells whose activity as macrophages is pronounced. The intravenous injection of azo dyes or colloidal metals causes these cells to be densely loaded. The participation on the part of the endothelium, however, is sharply limited to those definite tracts of it well within the hemal and lymphatic glands, etc." In another place he says: "But if either colloidal dyes or even suspensoids be let into the general blood-stream over a long period of time the stimulus is sufficient to give us a condition in which the vessels in all of the organs bearing specific endothelia (liver, lymph glands, hemal glands, marrow, spleen) are thronged with endothelial macrophages." Again he states: "While the vital stain substantiates the conception that the endothelium in five organs (lymph glands, liver, spleen, bone-marrow and hemal nodes) readily produces free intravascular macrophages, it does not support the contention that the extravascular macrophages have arisen in this way." We regret that Evans does not mention the particular species of mammals upon which his observations were based. In view of the unsettled state of opinion regarding the occurrence of hemal nodes in different animals it is extremely important to know upon what animals an author bases his observations.

Method

We decided, because of the existing uncertainty about hemal nodes, to work upon the sheep, an animal in which their occurrence is generally accepted. We used, in all, three lambs ranging from three to five weeks of age at the time of the experiments.

A suspension of carbon particles in acacia, available in the form of Higgin's Waterproof India ink, was used in

our experiments. The ink was filtered and diluted with an equal quantity of distilled water immediately before being used. The resulting suspension contained carbon particles ranging from 1 to 3 micra in size. It has been shown repeatedly in the rabbit and in the cat that when a small quantity (5 c.c.) of this carbon suspension is injected into the circulation of the living animal the particles cease to circulate in the blood-stream in 10 to 20 minutes and are deposited in the capillaries and in the sinusoidal spaces of the liver, spleen, lungs and bone-marrow. In these organs the particles are subsequently taken up by phagocytic cells.

The carbon suspension was injected directly into the jugular vein of the lambs which were anæsthetized for a few minutes with ether. Two of the lambs received an injection of carbon suspension on two successive days and were killed on the third day. They received, respectively, a total of 39 and 27 c.c. of carbon suspension. The third lamb received a single injection of 20 c.c. and was killed one and a half hours afterwards.

At autopsy, the animals under anæsthesia were bled to death through the right heart. A cannula was tied into the aorta and 10 per cent formalin was injected into the entire body. The abdomen was then opened and the entire carcass immersed in formalin for further fixation.

EXPERIMENTAL FINDINGS

Soon after injecting the carbon suspension into the jugular vein and allowing the animals to recover from the anæsthesia, we observed transitory dyspnoea and weakness. These are symptoms also seen nearly always in cats following injections of particulate matter, attributable undoubtedly to the rapid and large deposition of the foreign material in the capillary bed of the lungs. In the lambs these symptoms disappeared in less than an hour with complete recovery of the animals.

At autopsy, the blackening characteristic of such injections of carbon was observed in the lungs, liver, spleen and bone-marrow. The other tissues and organs, with the exception of the lymphoid tissue and hemal nodes which will be described presently, contained no carbon visible to the naked eye.

It was thought originally, when these experiments were planned, that it might be possible to make a sharp distinction between true lymph glands and hemal nodes on the ability of the latter alone to remove carbon particles from the circulation. It was hoped that, if the hemal nodes were true vascular organs, concerned in the phagocytosis of erythrocytes or other particles and possessing sinusoidal venous channels, they might resemble the spleen or liver in the property of removing particulate matter from the blood-stream. On the other hand, it was to be expected that the true lymph-glands would behave as in the rabbit and cat by showing little or no deposition of carbon in them after intravascular injections.* Furthermore, a pronounced difference in removal of carbon particles from the blood-stream would lend support of a physiological nature to those who believe that hemal nodes are functionally active structures.

It was at once obvious, upon examination of the lambs at autopsy, that the injection of carbon furnished no specific criterion for distinguishing between hemal and lymph glands. In the lamb which received a single injection of 20 c.c. of carbon, and was killed one and a half hours afterwards, the liver, spleen, lungs and marrow were black, but the lymphoid tissue and hemal nodes showed no black coloration. On the other hand, in the two animals which were injected twice and killed at the end of 48 hours, in addition to the liver, spleen, lungs and bone-marrow which were all intensely black, the entire lymphoid tissue and hemal nodes appeared grey. The Peyer's patches exhibited a greyish mottling. The tonsils and adenoid deposits of the naso-pharynx showed a similar coloration. This coloration was more pronounced in the lamb which had received the largest injection. The thymus had a greyish appearance in this animal alone.

When the blackening due to carbon deposition was used as a criterion, a distinction could not be made with the naked eye between lymph and hemal nodes. Many hemal nodes could, however, be identified in the retroperitoneal tissue by their chocolate color, due to a blending of the color of the blood and carbon within them. Large nodes, presumably lymphatic, in the inguinal and axillary regions were not as grey as the conspicuous mesenteric chains of glands, nor were these as grey as smaller nodes of uncertain character in the retrothoracic and retroperitoneal tissue.

We would like to point out, however, the contrast between hemal and lymph nodes on the one hand and the spleen. The spleen was deep black, the lymph and hemal nodes almost unblackened by contrast. It is of interest to compare this finding with observations made upon accessory splenic nodules. In the sheep we have not found any accessory spleens, but in cats and rabbits, into which carbon had been injected intravenously, we have frequently seen splenic nodules, located in the omentum in the neighborhood of the spleen, ranging from nodules just perceptible to the eye up to masses 6 or 8 mm. in diameter. These accessory splenic nodules, identified as such by microscopic sections subsequently, contained per unit volume as much carbon as the parent spleen. Accessory splenic tissue, therefore, is just as active in re-

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* After intravenous injection of 5 to 10 c.c. of carbon suspension into cats and rabbits no blackening of lymph nodes is observed, with the exception of a group of mediastinal and hepatic nodes which drain the lungs and liver. After injection of larger amounts (10 to 20 c.c.), the usual organs of deposition (liver, lungs, spleen and bone-marrow) having become saturated, traces of carbon become visible in the rabbit and cat in many tissues and organs, including the lymph glands and Peyer's patches.

moving carbon from the circulation as the spleen itself; hemal nodes by comparison are relatively inactive.

Microscopic.—The first lamb examined microscopically was the one which had received a single injection of 20 c.c. of carbon and was killed one and a half hours later. In the gross, liver, lungs, spleen and bone-marrow of this animal were black, but the lymph and hemal nodes showed no black coloration. Microscopic sections of the liver, lungs, spleen and bone-marrow revealed large quantities of carbon in the sinusoids and capillary beds of these tissues. The carbon in the spleen was scattered irregularly throughout the pulp and it could be observed that much of it had already been engulfed by free mononuclear cells. In the liver the carbon was almost entirely intracellular in the Kupffer cells and in the endothelium of the hepatic sinusoids. Frequently large masses of carbon-containing monocytes were seen in the lumina of the portal veins. It is presumable that these cells had arisen in the spleen and had reached the liver through the splenic circulation. The lungs showed tiny plugs of carbon in many interalveolar capillaries. In the bone-marrow carbon granules were observed in part free in the sinusoids, but predominately intracellular in the endothelial cells lining the blood-channels.

In the lymph and hemal nodes traces of carbon were occasionally observed. In the former, particles of carbon were encountered rarely in or on the surface of the endothelial cells lining capillaries or small venules. In the hemal nodes mononuclear cells containing carbon were seen infrequently in the venous lacunae.

The two other lambs which received several injections of carbon and were killed 24 hours after the last injection differed from the first only in the presence of carbon in the lymph and hemal nodes. The liver, spleen, lungs, and bone-marrow contained carbon in abundance as in the previous animal.

The lymph and hemal nodes differed markedly from those of the previous animal. In the lymph nodes the carbon occurred as numerous tiny black dots in the endothelial cells of many of the capillaries and venules. In places the vessels were strikingly outlined by the black stippling in their walls. The lymph sinuses usually contained no carbon, as might be expected after intravascular injection. But some lymph nodes, notably the ones draining the pulmonary and hepatic areas, as well as the mesenteric chain of nodes to a lesser extent, contained carbon-laden mononuclear cells within the lymph sinuses. It seems reasonable to suppose that, in these particular nodes, the carbon reached the sinuses, not by direct passage into them from the blood-vessels of the nodes, but indirectly by way of the afferent lymphatics.

Very occasionally carbon-containing mononuclear cells were observed lying free within the lumen of the blood capillaries. It is probable that these were monocytes of the circulating blood in passage through the capillaries or finding actual lodgment there. The lymph nodes draining the head, neck and extremities seldom contained carbon in the lymph sinuses and then only in traces. This is in keeping with the finding in the gross that these same nodes, though definitely grey, are less blackened than the nodes into which carbon drains through the afferent lymphatics.

On the whole, then, the lymph glands participate only slightly in the removal of carbon particles circulating in the blood-stream. Theirs is the duty primarily of filtering out and storing particulate matter which reaches them through the lymphatics. This can be easily demonstrated by injecting carbon particles into the subcutaneous tissue or one of the serous cavities of an animal, in which case the regional lymph nodes develop an extraordinary activity in removing the carbon from the lymph which is conveyed to them.

The hemal nodes in the two animals which received several injections contained considerable carbon. It was nearly all intracellular and in several different types of cells. It was most conspicuous in large, free, mononuclear cells which occurred most numerously in the lumina of the venous lacunae. Besides those in the lacunae, similar cells were encountered plentifully in the lymphoid tissue surrounding the lacunae and less frequently in the so-called blood-spaces or sinuses. The carbon formed large irregular clumps in the cytoplasm of these cells, which often entirely filled them, obscuring the nucleus. The mononuclear cells occurring in the blood-spaces were usually smaller than the ones seen in the venous lacunae or lymphoid tissue, and it is possible that the two types are of different origin. From the character of the nucleus it appeared as though the smaller cell might have been a detached and rounded up reticulum cell.

Giant cells possessing two or more nuclei, and extensive irregularly contoured cytoplasm, were also seen infrequently in the venous lacunae. In their cytoplasm they contained granular masses of carbon. These giant cells quite possibly arise by the fusion of several of the mononuclear phagocytes which we have described. Similar syncytial masses of cells are known to arise in the sinusoids of the liver following intravascular injections of bacteria or particulate matter.

In addition to this large conspicuous mononuclear cell containing carbon, the reticular cells covering the fibrous reticulum throughout the nodes, and which form branching trabeculae across the blood-spaces, contained fine black granules of carbon throughout their cytoplasm.

The eosinophile leucocyte, which occurs in considerable numbers in the hemal nodes of the sheep was the third cell element in which storage of carbon particles was observed. This observation surprised us, for we had never seen carbon within eosinophilic leucocytes before in any of numerous experiments upon animals. The carbon granules lay in these cells interspersed among the eosinophilic granules of the cytoplasm. In some nodes

the eosinophile cells contained little or no carbon; in other nodes there were about as many carbon granules as eosinophilic granules present in their cytoplasm. The eosinophile leucocytes which we encountered in the lymph nodes of the lamb did not contain carbon particles.

Polymorphonuclear neutrophile leucocytes were seen in the hemal nodes, but it was not observed that they contained carbon within their cytoplasm.

We have been unable to trace the origin of the conspicuous mononuclear cell containing carbon within the hemal node. It possibly is nothing more than a reticulum cell which has detached itself and become free. We thought that we saw in our sections reticular cells which were in process of detaching themselves. However, it is also possible that they may arise from the endothelial cells which one sees lining the venous lacunæ. We did not believe, however, that we saw much evidence of the endothelial cells rounding up or detaching themselves from the walls of the vessels. In fact, on following the outline of a venous lacuna under the high power of the microscope one could often see flattened endothelium everywhere seemingly inactive. These endothelial cells seldom contained granules of carbon in their cytoplasm. It is quite evident that, as long as they are sessile and unless they detach themselves, they play little rôle in phagocytosis.

A third possible origin for all or part of the phagocytic mononuclear cells that we have been describing in the lacunae is the circulation. It is not unlikely that the blood-stream conveys carbon-laden monocytes to the hemal nodes from the several organs (liver, spleen and possibly bone-marrow) in which it has been shown that they are liberated into the circulation.

DISCUSSION

It will be observed that, in spite of the fact that no differentiation could be made in the gross between lymph and hemal nodes on the basis of their behavior towards intravascular carbon particles, a distinct difference existed between lymph and hemal nodes on microscopic examination. The lymph nodes showed a different distribution of carbon and a cell reaction towards it different from that of the hemal nodes. In the lymph nodes the carbon was often deposited in minute particles in the endothelium of the capillaries and venules, as well as in large free mononuclear cells within the lymphatic sinuses. In the hemal nodes carbon, on the contrary, was deposited predominantly in the reticular cells and in large mononuclear cells occurring principally in the venous lacunæ and in the surrounding lymphoid tissue.

The question may be raised as to how we identified hemal nodes from lymph nodes. First of all the nodes in question fell into two groups on the basis of the microscopic findings which we have been describing. These two groups we further identified as lymph and hemal nodes, respectively, by the nature of their vascular patterns. The first group possessed the characteristic arborizing arteries and veins of lymph nodes, whereas the second group possessed the typical arrangement of venous lacunæ and veins characteristic of true hemal nodes. To obtain first-hand knowledge of the vascular relations existing within hemal and lymph nodes, we injected a freshly killed lamb through the heart with a suspension of India ink. We were able to confirm by this injection the striking differences which exist between the vascular pattern in the lymph and hemal nodes as Meyer ('14) has carefully worked them out in the lamb. The vascular arrangement studied in sections is an adequate means of differentiating lymph from hemal nodes in most instances, although, as Meyer has pointed out, there are some instances in which a decision as to the nature of the node can be arrived at only by an intranodal injection of a colored fluid to determine the presence or absence of lymphatics.

The next question of interest is to what extent our observations with carbon in the lamb agree with the findings for vital dyes by Goldmann ('09) and Evans ('15). We believe that there is justification for comparing the results of carbon injections with those of vital dyes, because there is a rather close parallelism between the two substances in the way they are phagocytized by the liver, spleen and bone-marrow after intra-vascular injection; and it is reasonable to suppose that the same parallelism holds true for hemal nodes.

As was pointed out in the introduction, Goldmann made his observations upon the rat, an animal in which the presence of hemal nodes has not been adequately established. His brief remark that pyrrhol blue is stored in the reticular cells throughout the nodes and that these cells often become free, wandering mononuclear cells within the blood-spaces, is substantiated by our observations. He did not observe, however, any of the other phenomena of deposition of particulate matter within the nodes which we have observed.

Evans does not mention upon what animals his observations were based, or how he identified the structures in question as hemal nodes. He states that the lymphatic sinuses of lymph glands and the venous sinuses of hemal glands are lined with endothelial cells whose activity as macrophages is pronounced. We are not certain whether he is referring here to the blood-spaces (also termed blood-sinuses) or the venous lacunæ (true venous sinuses), but from the context of the sentence we believe that the former is meant. Meyer says that in the lamb the reticulum of the blood-spaces is not lined with endothelium, a finding which we are able to confirm. Hence, if we understand Meyer correctly, we agree with him that, in the lamb, the confining walls and trabeculae of the blood-spaces are composed of reticulum cells associated with a reticular network, instead of a reticulum

with overlying endothelium such as one finds in the lymphatic sinuses of lymph nodes.

If Evans is referring to the true venous sinuses or venous lacunæ, our observations in the sheep, that these are nearly completely lined with endothelium, are identical with his and those of Meyer. In the sheep, however, we found the sessile endothelium rather inactive towards carbon particles, but it is quite possible that many of the heavily carbon-laden free mononuclear cells or macrophages and giant-cell syncytia observed within the lumen of the lacunæ originated from the endothelium of the lacunar walls. We are, however, unable, from our observations in the lamb, to ascertain with any certainty whether the endothelium of the venous lacunæ of the hemal nodes contributes to the formation of free intravascular mononuclear cells. The question for the present remains an open one. We have, however, seen free carbon-laden mononuclear cells in the veins draining hemal nodes, an observation substantiating Evans' finding that hemal nodes are a source of intravascular macrophages. Meyer also remarks that large mononuclear leucocytes are more numerous in the veins of the hemal nodes than in the arteries. He also notes that they are less frequent in the blood-spaces, an observation which we have confirmed, and which lends, we believe, some support to the possible origin of these cells, not from the reticulum of the blood-spaces, but from the endothelium of the lacunæ.

Summary

We have observed the phagocytic power of hemal nodes towards carbon particles injected into the blood-stream of the living sheep. Briefly, our results are as follows: Hemal nodes are capable of removing carbon particles from the circulation, but they possess this ability to a much lesser degree than the spleen. The carbon appears in the nodes in the form of coarse clumps within the cytoplasm of large mononuclear phagocytic cells. These cells lie in part free within the venous lacunæ, in part in the lymphoid tissue surrounding the lacunæ and less frequently in the so-called blood-spaces or sinuses.

Occasionally, multinuclear syncytial masses containing carbon are seen in the venous lacunæ. In addition to the conspicuous mononuclear cells which store carbon, the reticulum cells which occur throughout the nodes in association with the fibrous reticular network contain many small granules of carbon in their cytoplasm.

The distribution of carbon after intravascular injection differs in hemal nodes from that in lymph nodes. The lymph nodes in the lamb take up only a little carbon from the blood-stream and that in the form of small granules in the endothelium of some of the capillaries and venules. Whenever carbon escapes from the blood-vessels, it reaches the regional nodes through their afferent lymphatics, in which case it is taken up by innumerable mononuclear cells within the lymphatic sinuses.

As has been mentioned, the hemal nodes do not remove carbon from the circulation as quickly, nor to nearly the same extent, as does the spleen. Accessory spleens have not been observed by us in the sheep, but in cats and dogs, in which we have frequently noticed them, it is seen that accessory splenic tissue is identical with the principal spleen in its behavior towards carbon particles.

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THE EFFECT OF PYROGALLIC ACID UPON CONNECTIVE-TISSUE CELLS OF THE CHICK EMBRYO IN TISSUE CULTURES

By John T. Bauer

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Investigators have employed various means to ascertain whether oxidation proceeds in the nucleus or in the cytoplasm of the cell. Lillie (1913), by the use of a-naphthol and paradiamidobenzene upon the frog's corpuscles, found that a precipitate of indophenol occurred at the interface between the nucleus and cytoplasm, and near the outer surface of the cell just within the plasma membrane. Since α-naphthol and paradiamidobenzene form a violet-colored precipitate of indophenol by a union with oxygen, Lillie suggests that this "indicates the existence of a general relation of the cell's surfaces or protoplasmic phase boundaries to oxidations."

Osterhout (1917), with Indian pipe (Monotropa uniflora), found that in torn pieces of the thin leaves the cells nearest the cut edge showed a marked discoloration within the nuclei in the presence of oxygen. When the supply was diminished, the time necessary for this discoloration to occur was increased. This he regarded as an indication of a marked activity of oxidation within the nucleus.

It has been known to chemists and others interested in experiments requiring an atmosphere free from oxygen that one of the simplest means of obtaining this condition is by absorbing the oxygen with alkaline pyrogallic acid.

The ease with which it unites with oxygen makes it a substance frequently used in gas analysis. It not only possesses the property of uniting with uncombined oxygen, but it is also capable of reacting with the exposed photographic plate and reducing the light-affected silver salts to free silver. In doing so, there is formed a compound with oxygen which is easily detected by a characteristic change in color. From a clear, colorless fluid (or, in the case of the so-called pyro-developer, from a pale brown color) the reaction is marked by a change to an intense reddish brown color. This characteristic makes pyrogallic acid an excellent detector of oxygen in a free or loosely combined form. This study was undertaken in an effort to see what effect pyrogallic acid had upon cells in tissue-culture, with special reference to the possibility of determining the site of intracellular oxidation and reduction.

I wish to express my gratitude to Dr. and Mrs. Lewis for their aid and suggestions given me in this investigation, which was carried out in their laboratory.

MATERIALS AND METHODS

Most of the observations were made upon normal connective-tissue cells of chick embryos, six and seven days old, grown in Locke-Lewis solution from one to nine days.

The pyrogallic acid was placed in the cavity of the slide in a crystalline form in such a manner that the rays of light could pass unhindered to the growth and thence through the objective. Care was taken so that none of the crystals projected into the fluid and growth on the coverslip. No attempt was made to standardize the quantity of pyrogallic acid, a few crystals being sufficient to produce changes slow enough to be studied. A few slides were treated with a little dilute sodium hydroxide solution and pyrogallic acid, but the color changes within the fluid in the bottom of the slide, and later in the hanging drop, were so great, owing to the absorption of oxygen from the air in the cavity, that the growth was masked and the method was therefore abandoned.

While most of the cultures were studied unstained, several were treated with brilliant cresyl blue, janus green, neutral red, and methylene blue (Ehrlich's rectified). The last was used most extensively because of its loss of color by reduction and its return again by reoxidation.

The normal growth and the vitally stained preparations were always studied first under an oil-immersion lens, after which the coverslip was removed, the pyrogallic acid placed in the hollow of the slide and the preparation again sealed on the vaseline ring and studied immediately in a warm box (39°C.). An attempt was made to follow the same cells throughout the various steps of the experiment, but this was found difficult because of the tendency on the part of the cells to contract.

SEQUENCE OF CHANGES

The cells along the border of the growth were the first to exhibit changes, unless the pyrogallic acid happened to be located to one side of the growth, in which case the border nearest the pyrogallic acid showed the first change.

No general statement can be made concerning the time necessary to produce changes. This depended upon the amount of pyrogallic acid applied and the distance between it and the growth. If the pyrogallic acid accidentally touched the Locke-Lewis solution, it was immediately absorbed and by the time it was possible to focus upon the growth, all the cells were dead.

The first changes consisted in cessation of movement of the mitochondria and indications of coagulation of the nucleoplasm, followed by that of the cytoplasm. The formation of a distinct nuclear membrane then occurred, and some time later the nucleus became slightly brown.

Changes in the Nucleus.—The nucleus in the normal living tissue-culture cell can be recognized as such because it is more homogeneous than the cytoplasm and has a slightly different index of refraction, with a delicate, hardly definable membrane around it, within which lie one or two more opaque bodies, the nucleoli. Granules, mitochondria, and neutral-red bodies in the cytoplasm aid in outlining it more distinctly.

The application of pyrogallic acid led to a diffusely granular coagulation of the homogeneous nucleoplasm. This granular deposit later became coarser and more prominent. At last, hours after the application of the acid, this became an uneven, often moniliform structure, consisting of coarse granules of all sizes and shapes. Little change was noted thereafter, this condition remaining for days. The cells appeared as though they had been fixed, but subsequent treatment with dehydrating and staining agents showed that this was not the case.

One of the best indications of the effect of pyrogallic acid upon the cells was the conversion of the delicate, almost invisible nuclear membrane into a highly refractive line recognized with the utmost ease. This change in the nuclear membrane is an indication of cell death (Lewis and McCoy, 1922). The nuclear membrane, when accentuated by death, was constant throughout all the cells and always remained until the growths were discarded.

Very few changes were noted in the character of the nucleolus. From a substance slightly more opaque than the surrounding nucleoplasm, it became less and less opaque until almost invisible.

One of the most characteristic changes was the formation of a brown color in the cells. It arose subtly and was never deep enough to be observed until after the other changes had taken place. From a faint, pale yellowish brown, it became deeper until it reached its maximum as a light brown. The color in the nucleus was always

deeper than in the cytoplasm. When the pyrogallic acid had previously been made faintly alkaline with sodium hydroxide, the same degree of color difference between the cytoplasm and nucleus appeared, but the depth of color in both was greater than with pyrogallic acid alone.

In general, there was little change in the shape of the nucleus. No nuclear extrusions, such as Lewis (1921) found when potassium permanganate was placed upon similar cells, were noted.

Changes in the Cytoplasm.—The cytoplasm of a normal connective-tissue cell in tissue cultures is a thin, flattened layer of protoplasm, slightly more opaque than the surrounding medium and showing in places a faint border. Within the cytoplasm, according to the age of the culture and certain nutritive factors, are seen granules, vacuoles, fat globules, and mitochondria. These cells usually form a loose network of long, irregularly shaped cells, each separate and distinct, flattened out to conform to the medium in which they grow, their protoplasmic processes touching, but not confluent.

An application of a small amount of pyrogallic acid caused marked changes in the surface tension of the cells. A general rounding of the protoplasm occurred, connections with neighboring cells were withdrawn, and the protoplasmic projections dwindled to mere fibrils waving in the fluid. This rounding up of the cell was often attended by the extrusion of blebs, more fluid and quite globular, which never became detached from the cell giving rise to them. Often the outer layer of cells retracted upon the growth, rounding up to such an extent that further observations upon the contents of the cell were impossible.

However, not all cells retracted to such an extreme extent as these. There were cells in which the application of pyrogallic acid was attended by little change or bleb formation, and these were used for study.

Concurrent with the granulation of the nucleus, a similar phenomenon occurred in the cytoplasm, although it never became as coarsely and irregularly granular as the nucleus.

Mitochondria normally are faintly, though distinctly more refractive than the cytoplasm. They are of various sizes and shapes and usually are in motion, swaying or twisting and showing slow progression. Upon the application of pyrogallic acid the first variable effect was their loss of motion. They later disintegrated by breaking into small particles or forming vesicles. The longer mitochondria often swelled in several places, became segmented, each particle assuming a spherical shape and becoming obliterated by cytoplasmic changes. A number of changes thus occurred, but the final result was always a disintegration marked by a diminution of their refractivity.

Fat globules were never stained by pyrogallic acid.

Results with Stains.—In cells which had previously been treated with vital dyes, a loss of color always resulted when pyrogallic acid was added. Sometimes the dye became diffused throughout the cell and medium, while in other cases it disappeared entirely. In several instances the mitochondria were stained with janus green before a study of the effect of pyrogallic acid was attempted. In such stained cells the behavior exhibited by the mitochondria was practically the same as in the unstained preparation—the color disappeared from them at about the time they lost their motion.

One of the most interesting effects of the pyrogallic acid observed was in the vacuoles and granules. These structures are seen mostly in senile cultures (Lewis, 1919). They are of various sizes and usually tend to accumulate about the centrosphere, at one side of the nucleus, and often surround the latter. They are stained by neutral red, brilliant cresyl blue and methylene blue. In the study of these bodies, most of the cells had been previously stained with methylene blue, and all of the vacuoles and granules were blue. When pyrogallic acid was applied, it was noted that some of the stained bodies turned gradually to violet, red, finally pink, and then disappeared. Others remained blue, holding their color for a long time and disappearing without an intermediate change to red and pink. Channels, red or pink in color, also appeared in the cytoplasm and then disappeared. The addition of pyrogallic acid to a solution of methylene blue in Locke-Lewis solution did not result in a change of color *in vitro*.

Discussion

It is difficult to say, upon exposing a living cell to a decreased amount of oxygen by means of some such substance as pyrogallic acid, how much of any resulting change in structure is due to the function of the structure in regard to oxidation and reduction, how much to the actual oxidation and reduction of the structure itself, or how much to the toxic effect of the substance, quite apart from a decrease in the amount of oxygen available for the cell. So long as the cell continues to survive and multiply, it would seem certain that any change is due to the activity of the cell itself and indicates the function of the structure, in regard to the amount of oxygen supplied, on the substance added. If, however, the cell shows signs of degeneration or dies, it raises a doubt as to whether the cell itself is playing an active rôle at all. The ultimate result of the application of pyrogallic acid was death. Death was not due to a change in the hydrogen-ion concentration of the medium in which the cells grew, because the pH always remained within the limits capable of sustaining life (M. R. Lewis and L. D. Felton, 1922). The changes occurring after the application of pyrogallic acid, to stained cells especially, seemed to indicate that death was due to a difference in the oxygen supply rather than to the toxic nature of the substance itself.

In a living fibroblast, granules, vacuoles and mitochondria are colored upon the addition of vital dyes, while the nucleus and cytoplasm remain colorless. The latter may act as a reducing agent and convert the dye into a colorless compound by the withdrawal of oxygen, as can be performed experimentally by reducing agents in the case of methylene blue and neutral red (Plato, 1900). When this colorless dye reaches the granules, it again meets oxygen, and color returns in these bodies.

With the addition of pyrogallic acid to the cavity beneath the living cells, the mitochondria ceased to move and tended to straighten out, indicating a paralysis of the cytoplasm. This perhaps was due to the sudden disturbance in the oxygen balance, as the color began to fade from them. This also occurred with the granules and vacuoles, although it must be remembered that these structures themselves became less distinct until they were no longer visible. The cells became gradually less reducing as death approached. When death occurred, and the cytoplasm and nucleus became granular and the nuclear membrane more refractive, a diffuse blue color appeared throughout the entire cell. As dead cells absorb oxygen readily, it appears as though the cell at this moment ceased to reduce and so contained sufficient oxygen to give color to the dye which permeated the cells. Not all cells became diffusely colored and this can perhaps be explained on the assumption that the pyrogallic acid was absorbing oxygen simultaneously with and more rapidly than the dead cell, so that little accumulation of oxygen was possible within the cell. As more and more oxygen was absorbed by the pyrogallic acid, and the latter became diffused throughout the culture medium, the dead cells gave up some of their oxygen at the expense of the dye and became gradually brown, the color of the oxidation products of pyrogallic acid. At times there seemed to be a fusion of the blue color with the brown color of the pyrogallic acid oxidation products, with the formation of a diffuse greenish brown color, indicating the absorption of oxygen by both the pyrogallic acid and dye. While it is possible that the greater degree of color within the nucleus may be due to a more intense absorption of oxygen by this body, it can perhaps be explained on the basis that the density of the protoplasm is greater here than anywhere else.

The results of Osterhout's experiments with Monotropa uniflora can probably be explained as the absorption of oxygen by dead tissue and an oxidation of the cell upon its death.

SUMMARY

1. Pyrogallic acid is toxic to tissue-culture cells, as indicated by the paralysis of the cell followed by precipitation of cytoplasm and nucleus with the formation of a distinct nuclear membrane.

2. Pyrogallic acid does not give definite evidence concerning the site of intracellular oxidations and reductions.

3. The application of pyrogallic acid to a vitally stained cell results in the disappearance of the dye from the mitochondria, granules, and vacuoles, presumably due to a withdrawal of oxygen.

4. Death of the cell results in an increased absorption of oxygen, first indicated by a diffuse blue coloration of the entire cell when previously stained by methylene blue or janus green, sometime later giving place to a brown color of the nucleus and cytoplasm, the former more intense than the latter.

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A CASE OF CARCINOMA OF THE FOURCHETTE

By Leo Brady, M. D.

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Cases of carcinoma of the vulva, while not extremely rare, are rather uncommon. There have been one hundred and sixty-five thousand admissions to the Johns Hopkins Hospital since it opened, and of these twenty-nine thousand have been assigned to the gynecological service. Among these twenty-nine thousand there have been nineteen instances of primary carcinoma of the vulva. To mention that during this same period we have had seven hundred and fifty-six cases of carcinoma of the cervix gives, perhaps, the best idea of the relative frequency of this condition.

These nineteen malignant growths of the vulva arose in the following situations: Six from the clitoris, one from a Bartholin's gland, two from the urethra, five from a labium majus, one from a labium minus, one from the fourchette, and four were indexed simply as carcinoma of the vulva. In these last four, when the patient was first seen, the growth was so extensive that it was impossible to tell exactly where it had originated. All the carcinomas except two were found, under the microscope, to be squamous in type. These two were adenocarcinomas, showing a definite glandular arrangement. One was the case in the series known to have arisen from a Bartholin's gland, the other was too far advanced to permit of a more definite conclusion being reached as to its origin than that it had arisen from the vulva. However, as it is generally believed that practically all cases of adenocarcinoma of the vulva arise from a Bartholin's gland, probably one of these structures was also the starting-point for this neoplasm.

After studying the above statistics, I decided that the case of primary carcinoma of the fourchette which I recently met with in private practice was of sufficient interest to warrant reporting. At the same time I have made a study of the nineteen cases of primary carcinoma of the vulva in the Johns Hopkins Hospital series and shall first give in brief the results of this work.

The average age of these nineteen patients on admission was fifty-seven years. The youngest patient entering the hospital for this condition was a colored woman, aged 35, with a primary carcinoma of Bartholin's glands; the oldest, a woman, aged 87, with a primary growth of the left labium minus. That 13 of the 19 patients (68%) were fifty years of age or over shows that we are dealing with a condition primarily of advanced life. Two of the patients were colored; seventeen were white. As one colored woman is admitted on the gynecological service for every three white, we can at least conclude that carcinoma of the vulva is not especially common among negroes.

The symptoms of this condition are four: tumor, a watery labial discharge, irregular bleeding and pain, these usually coming on in the above order. In some instances the tumor is noticed by the patient a long time before other symptoms develop. One woman had noticed a lump on her vulva for eight years before coming to the hospital, another for seven, two others for three; and yet, on examination, all of these patients were found to have tumors that were still operable. It is, of course, impossible to be sure that all these growths were primarily malignant, and yet we can feel certain that the onset of this condition must be very gradual. We found that seventeen months was the average time that had elapsed in this series between the time the patient first noticed that anything was wrong with her and the time she came to the hospital for her examination.

Sixteen of these patients were considered, on admission, to be operable, three inoperable. In spite of the long duration of symptoms, then, operation was still considered to offer a large proportion of these patients a reasonable hope of cure; and this is very encouraging. This finding is in sharp contrast with our experience with carcinoma of the cervix.

Bleeding is a late symptom and occurs only after ulceration has taken place. It had never been present more than a few months in the operable cases, and usually had not occurred at all. In one absolutely hopeless case, it had been present eleven months.

Pruritus vulvae, with the inevitable scratching, was present in 50% of these cases; it had usually been present for many years and long before a tumor had been noticed. It seems quite probable that the irritation resulting from the scratching is an etiological factor in carcinoma of the vulva.

Contrary to the usually accepted ideas, enlarged inguinal glands were found but rarely—in only three cases in this series. One of these was an inoperable case; in the other two, the glands were removed at the same time that a vulvectomy was done.

As the first patient in this series was operated on in February, 1890, and the last one, excluding the case I had recently, in May, 1921, there has been considerable variation in the operative procedure. In some cases the growth with a wide margin of tissue was removed, in others the procedure was more radical and a total vulvectomy was carried out, while in three others a total vulvectomy, combined with the removal of the inguinal glands on both sides, was the operative procedure. In only one case was the urethra removed, and as in that

Fig. 1.—Microphotograph showing change from normal to cancerous tissue. Note how slight has been the invasion into the surrounding tissue.

instance incontinence resulted and it seemed improbable that all the carcinoma was taken out, such a radical procedure seems hardly justified. In some instances the knife was used, in others, the cautery. Radium was used on one patient.

At the present day the usual operation is excision of the growth with a wide margin of tissue combined with the removal of the inguinal glands on both sides. Probably the cautery is to be preferred to the knife. In one case of carcinoma of the upper portion of the labium majus operated upon by Dr. Cullen, he made a wide dissection of the inguinal regions and then, with the cautery, removed the carcinomatous growth, giving it a wide margin. The inguinal tissues and the growth were finally removed in one piece, the healthy tissue that had been burnt with the cautery being cut away with the knife. Dr. Cullen felt that by this technique the transplantation of cancer cells was reduced to the minimum. When the growth is primary in the fourchette, it is questionable whether the removal of the inguinal glands is indicated. In my own case I was satisfied with the wide removal of the growth, followed six weeks later by intensive radiation to both groins and to the original site of the neoplasm.

Mrs. J. C., aged 35, seen April 5, 1923.

The patient was married at the age of 14; at 17 she contracted from her husband syphilis and a Neisser infection. She had been treated almost constantly from that time. She had had about forty doses of salvarsan, as well as numerous courses of mercury and iodide. In 1915 a double salpingectomy had been done through a midline incision, and almost immediately afterwards a post-operative hernia had developed. In 1913—ten years after the contraction of the syphilitic infection—the patient had developed a lesion on the vulva. This lesion had persisted from that time and had slowly increased in size. There had been no noticeable increase in rapidity of growth during the last few years. Ever since the tumor first appeared the patient had been under medical attention. She had received, during this time, between seventy-five and a hundred local applications to the vulva. There had been no history of any vaginal discharge, irregular bleeding or pain.

Examination: April 1, 1923.—The patient is a well nourished young woman. The general physical examination is essentially negative. There is a lower abdominal midline scar from the previous operation through which a large hernia protrudes. Examination of the abdomen is otherwise negative. The inguinal glands are not enlarged on either side. On pelvic examination the following is found: At the junction of the skin and mucous membrane, on the lower border of the vulva and extending forward, there is an indurated area about 4 c.c. in length. In the centre of the induration there are what look like three or four cracks, but there is very little ulceration, and no bleeding occurs on examination. The edges of the area are not overhanging, nor has the lesion a punched-out appearance. There is very little loss of tissue. The Wassermann test is negative.

Diagnosis.—It was my impression that the lesion was inflammatory in character. It seemed quite likely that it had developed in an old luetic lesion and that the numerous local applications which the patient had received had prevented healing from taking place. The history of numerous salversan treatments without any effect on the lesion, combined with the negative Wassermann, practically ruled out the possibility that the present condition was syphilitic. If the condition had been either tuberculosis or granuloma inguinale, there should have been more loss of tissue. Despite the chronicity of the condition malignancy was considered possible and an appropriate operation was thought to be indicated.

Operation: April 8, 1923.—The post-operative midline hernia was first corrected. The vulval lesion was then removed with a wide margin of tissue on all sides. In removing the fourchette the operator carried the dissection down as close to the rectum as was possible and quite far anteriorly, removing a large part of both labia majora and labia minora. In six weeks the perineal wound had healed up completely with no evidence anywhere that any malignancy had been left. I had radium applied to the perineum and inguinal glands so as to give the patient every possible chance.

Dr. Wm. G. MacCallum examined the microscopic slides from this tumor and made the following note: "The specimen shows an epithelioma with a great deal of keratinization. The strands of cells extend only a short way down into the underlying tissue and in general the tumor is pretty sharply outlined. It has not the appearance of a basal cell epithelioma, but is distinctly squamous in character." The micro-photograph shows the change from normal to cancerous tissue. It also shows how little invasion has occurred into the surrounding tissue.

The age of the patient, the site and the extreme chronicity of the lesion, which under the microscope is defintely malignant, make this case of sufficient interest to justify a report.

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